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ERRATA.

VOL., 1947.

Page	Line	
383	11*	*for* "*N*-benzyl-*N'*-methylbenzamidinium hydrochloride" *read* "*N*-benzyl-*N'*-methylbenzamidinium chloride".
386	6*	*for* "(2·65 g. or 48%)" *read* "(5·15 g., 93%)".
388	28	*for* "N-*benzyl*-N'-*methylbenzamidine*" *read* "N-*Benzyl*-N'-*methylbenzamidine*".
499		In the last line of the formulæ, *for* "= *p*-Me·C_6H_4)" *read* "(T = *p*-Me·C_6H_4)".

* From bottom.

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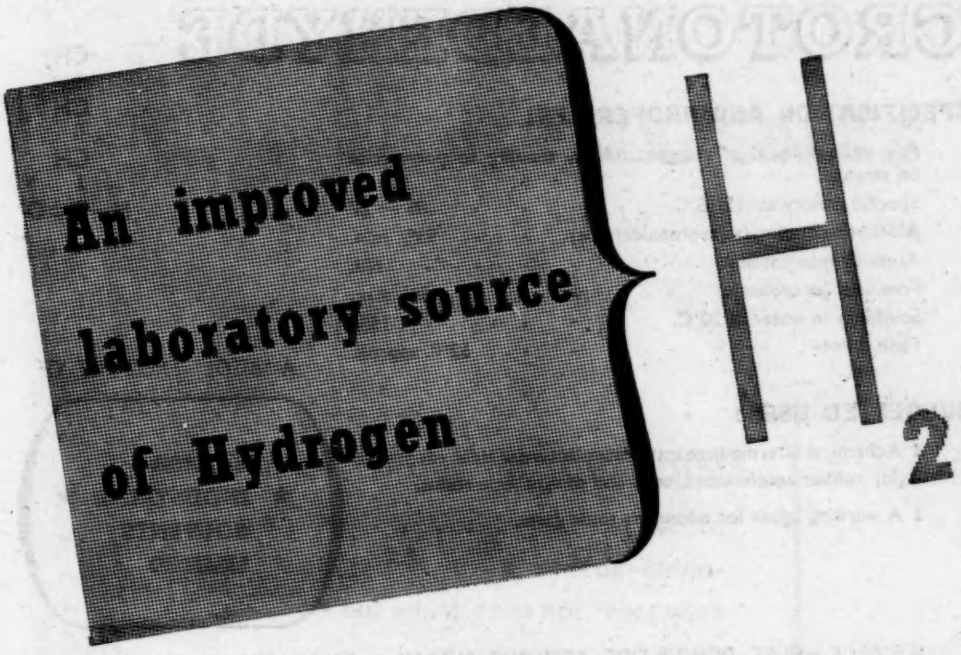

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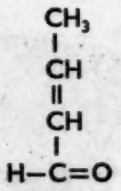

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164. *The Crystal Structure of Strontium Azide.*

By F. J. Llewellyn and F. E. Whitmore.

The structure of strontium azide has been completely determined by means of three-dimensional Fourier sections and lines using all the $\{hkl\}$ structure amplitudes obtainable with Cu-$K\alpha$ X-radiation. The structure is ionic, each strontium ion being surrounded by 8 azide ions, arranged in two sets, at distances 2·63 and 2·77 A., severally. The azide ion is linear and symmetrical, the nitrogen–nitrogen separation being 1·12 A.

The azide grouping (N_3) has been shown by X-ray and electron-diffraction studies to be linear in both electrovalent and covalent substances. In the former, typified by sodium and ammonium azides (Frevel, *J. Amer. Chem. Soc.*, 1936, **58**, 779; *Z. Krist.*, 1936, **94**, *A*, 197) the two nitrogen–nitrogen separations in the azide ion are equal; the ion resonates between the three structures (*a*), (*b*), and (*c*),

(*a*) $\bar{N}{=}\overset{+}{N}{=}\bar{N}$ (*b*) $N^{\bullet-}{-}\overset{+}{N}{\equiv}N$ (*c*) $N{\equiv}\overset{+}{N}{-}N^{\bullet-}$

each of which is equally important, and stabilisation is effected by the considerable resonance energy; the nitrogen–nitrogen separation is 1·15 A. In the latter case, typified by cyanuric triazide (Knaggs, *Proc. Roy. Soc.*, 1935, **150**, *A*, 576), these two nitrogen–nitrogen bonds are not equivalent and the azide grouping has the dimensions shown in (I).

R—N—N—N
1·26 1·11
(I.)

The three most probable resonance forms for the covalently linked azide group are (*d*), (*e*), and (*f*):

(*d*) $R{-}N{=}\overset{+}{N}{=}\bar{N}$ (*e*) $R{-}\bar{N}{-}\overset{+}{N}{\equiv}N$ (*f*) $R{-}\overset{+}{N}{=}\overset{+}{N}{-}N^{\bullet-}$

the last probably does not contribute to any appreciable extent, for it involves adjacent positive charges which render this form more unstable. Resonance therefore occurs between (*d*) and (*e*), leading to an unsymmetrical grouping of lower stability than the azide ion.

The stability of metallic azides to heat, friction, and impact varies considerably and is determined, at least in part, by the bonding between the metal and the azide group. Thus, the alkali-metal azides, which are ionic, are stable both to friction and to impact and are only decomposed gently by heat at 300—400°. The alkaline-earth azides are decomposed more violently by heat at a lower temperature (*ca.* 110—160°) but remain insensitive to friction and impact. On the other hand, azides of the heavier metals, *e.g.*, lead, and those of many of the B-sub-group elements, *e.g.*, copper and silver, decompose sometimes with explosive violence when lightly struck or rubbed.

Between these two extremes there is a large number of azides of intermediate properties in which it may be assumed that the linkage of the azide group is more or less covalent. The following investigation of the structure of strontium azide is the first of a series in which it is hoped to trace the development of covalent bonding with increasing instability.

Preliminary Crystallographic Data.—Small, well-defined, orthorhombic, bipyramidal (pseudo-tetragonal) crystals of strontium azide exhibiting the form {111} were obtained by slowly evaporating the aqueous solution to dryness in an Erlenmeyer flask. Single-crystal rotation photographs using Cu-$K\alpha$ X-radiation gave the cell dimensions: $[a] = 11{\cdot}82$, $[b] = 11{\cdot}47$, $[c] = 6{\cdot}08$ A. Oscillation photographs about the three principal axes revealed the halvings $\{hkl\}$ absent when $h + k \neq 2n$, $k + l \neq 2n$, $h + l \neq 2n$; $\{0kl\}$ absent when $k \neq 2n$, $l \neq 2n$, $k + l \neq 4n$; $\{h0l\}$ absent when $h \neq 2n$, $l \neq 2n$, $h + l \neq 4n$; and $\{hk0\}$ absent when $h \neq 2n$, $k \neq 2n$, $h + k \neq 4n$. The space-group is therefore F_{ddd}. The observed density is 2·73 g./c.c.; calculated for eight molecules in the unit cell, 2·77 g./c.c.

The space-group F_{ddd} accommodates 32 general positions, five sets of 16-fold special positions, and two sets of 8-fold special positions. Since there are 8 strontium ions in the unit cell, these must be located in one of the sets of 8-fold special positions, and because the choice between these is arbitrary, the co-ordinates may be written down as (000), $(0\frac{1}{4}\frac{1}{4})$, $(\frac{1}{4}0\frac{1}{4})$, $(\frac{1}{4}\frac{1}{4}0)$, $(\frac{1}{4}\frac{1}{4}\frac{1}{4})$, $(\frac{3}{4}\frac{3}{4}\frac{1}{4})$, $(\frac{3}{4}\frac{1}{4}\frac{3}{4})$, $(\frac{1}{4}\frac{3}{4}\frac{3}{4})$.

The azide grouping can conveniently be dealt with in two parts: (*a*) the central nitrogen atoms, of which there are 16, must lie in one of the 16-fold special positions; and (*b*) the end nitrogen atoms, of which there are 32 located in the general positions, or in two sets of 16-fold positions.

(*a*) The five sets of 16-fold positions can be classified into two kinds; the first is centro-

symmetrical, and the second possesses two-fold axial symmetry. Thus, whatever the actual position of the azide group, it must possess either a centre of symmetry or a two-fold axis.

Measurement of Intensities.—The intensities of the diffracted beams from all the planes {*hkl*} observed by using Cu-$K\alpha$ *X*-radiation were obtained by visual estimation using a simple comparator on which a number of photographic spots produced by beams of known intensity had previously been recorded. From these intensities a set of structure amplitudes, on an arbitrary scale, can be obtained by using the relation $F = k\sqrt{ID\phi/L}$, the symbols of which are defined in an earlier paper (this vol., p. 838).

Usually it is convenient to render a set of relative structure amplitudes absolute by comparing directly a number of diffracted beams with some standard beam—normally the 400 reflection from the ground cleavage face of rock-salt. In this particular case we did not consider this to be necessary since the phases of nearly all the structure amplitudes could be deduced from the known position of the strontium atoms. When the structure was completed, the experimental structure amplitudes were made absolute by multiplying by the factor $F_{calc.}/F_{obs.}$. The table includes a list of the experimental structure amplitudes and also the calculated phases and structure amplitudes.

hkl.	$F_{calc.}$	$F_{obs.}$	*hkl.*	$F_{calc.}$	$F_{obs.}$	*hkl.*	$F_{calc.}$	$F_{obs.}$
004	123	169	335	45	93	711	37	99
022	278	250	351	62	124	713	86	112
026	273	184	353	140	167	715	39	69
040	347	268	355	141	122	731	12	66
044	224	188	371	117	133	733	98	104
062	296	239	373	121	143	735	16	95
066	140	118	375	60	84	751	128	108
080	99	161	391	69	120	753	35	55
084	311	195	393	123	114	755	0	37
0, 10, 2	246	186	395	36	65	771	50	99
0, 12, 0	157	173	3, 11, 1	43	83	773	48	57
111	62	114	3, 11, 3	118	85	791	67	81
113	118	152	3, 13, 1	120	95	793	33	49
115	65	97	400	−71	<20	7, 11, 1	96	116
117	65	58	404	217	177	800	417	309
131	55	58	422	156	160	804	107	116
133	109	142	426	22	81	822	211	179
135	93	119	440	100	148	840	260	188
151	128	175	444	103	107	842	192	124
153	28	73	462	73	114	862	238	172
155	4	62	480	233	199	880	88	142
171	120	138	484	−22	56	8, 10, 2	216	144
173	83	79	4, 10, 2	48	98	911	16	91
175	25	81	4, 12, 0	115	88	913	97	95
191	79	118	511	193	168	915	34	73
193	46	76	513	76	113	931	10	67
195	47	73	515	110	115	933	76	82
1, 11, 1	92	118	531	199	191	935	56	85
1, 11, 3	70	63	533	107	110	951	72	102
1, 13, 1	10	46	535	69	83	953	19	48
202	233	208	551	89	98	971	63	95
206	155	144	553	142	140	973	−21	134
220	285	250	555	127	111	991	70	86
222	124	100	571	99	112	10, 0, 2	172	151
224	132	184	573	143	123	10, 2, 0	247	152
242	211	188	575	78	64	10, 2, 4	130	113
246	143	127	591	73	106	10, 4, 2	180	115
260	195	191	593	143	94	10, 6, 0	142	148
262	130	59	5, 11, 1	87	80	10, 8, 2	133	123
264	168	150	602	183	184	11, 1, 1	73	114
282	174	173	606	89	138	11, 1, 3	72	73
2, 10, 0	144	165	620	134	248	11, 3, 1	134	113
2, 10, 4	148	109	622	−101	60	11, 3, 3	53	64
2, 12, 2	140	110	624	161	146	11, 5, 1	127	71
311	164	228	642	156	150	11, 7, 1	94	97
313	86	124	646	113	127	12, 0, 0	−14	44
315	114	219	660	176	177	12, 2, 2	66	107
317	115	120	682	118	150	12, 4, 0	87	97
331	214	232	6, 10, 0	153	152	13, 1, 1	132	96
333	76	121	6, 10, 2	153	152	13, 3, 1	120	94

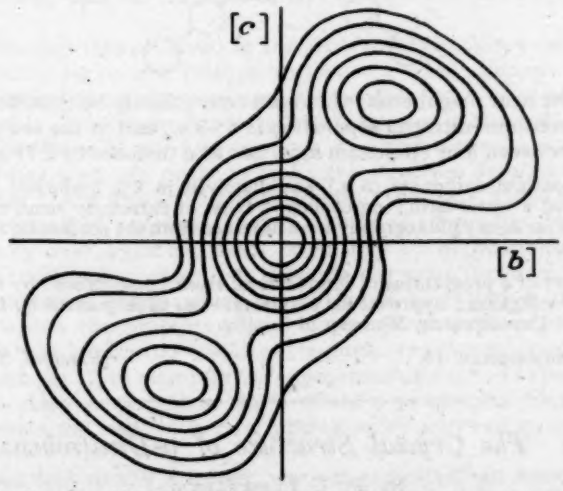
Determination of the Structure.—The strontium atoms located at (000), etc., will be in phase and contribute to all the observed (*hk*0), (*h*0*l*), and 0*kl*) planes. Since the contributions of the

strontium atoms will in general be greater than that of the nitrogens, as a first approximation, the phase of these planes was taken as 0°, or, in other words, these structure amplitudes are positive. A Fourier projection on the *c*-plane using all the *hk*0 structure amplitudes was therefore computed in order to determine the approximate co-ordinates of the atoms of the azide group. Two peaks were observed having (*xy*) co-ordinates (0·125, 0·000) and (0·125, 0·075). It therefore appeared likely that the central nitrogen atom was located on the two-fold axis which passes through the origin and is parallel to the [*a*] axis. That the atoms of the azide group have *x* co-ordinates approximately equal to 0·125 is indicated by the relative magnitudes of F_{400} — very small, F_{800} — very large, F_{1200} — very small; F_{h00} being calculable by the equation

$$F_{h00} = 8f_{Sr} + 16f_{N\ centre} \cos 2\pi hx + 32f_{N} \cos 2\pi hx$$

Having thus established that the central nitrogen atom lies along the [*a*] axis, two possibilities arise: the peak observed at (*xy*) co-ordinates (0·125, 0·000) may be due to an atom having (*xyz*) co-ordinates (0·125, 0·000, 0·000) leading to the 16 positions (0·125, 0·000, 0·000), (— 0·125, 0·000, 0·000), (0·375, 0·250, 0·250), (0·125, 0·250, 0·250), (0·125, 0·500, 0·500), (— 0·125, 0·500, 0·500), (0·375, 0·750, 0·750), (0·125, 0·750, 0·750), (0·625, 0·000, 0·500), (0·375, 0·000, 0·500), (0·875, 0·250, 0·750), (0·625, 0·250, 0·750), (0·625, 0·500, 0·000), (0·375, 0·500, 0·000), (0·875, 0·750, 0·250), (0·625, 0·750, 0·250), or to an atom at (0·375, 0·000, 0·000) leading to 16 positions as above. It will be readily seen that these two possibilities reduce to the same set of (*xy*) co-ordinates.

FIG. 1.



The atomic co-ordinates (0·125, 0·000, 0·000) for the central nitrogen are extremely improbable since the separation from the strontium atom at the origin would then be only 1·47 A., considerably less than the sum of the Sr^{2+} and N^{-} radii. Attention was therefore directed to the other possibility in which the two nitrogen atoms have the approximate co-ordinates

$$N_{1\ centre}\ 0{\cdot}375\ \ 0\ \ 0 \qquad N_2\ \ 0{\cdot}375\ y\ z$$

The three-dimensional Fourier line, parallel to the [*a*] axis, passing through the point $z = 0$, $y = 0$ showed a large maximum at $x = 0{\cdot}375$. A three-dimensional Fourier section parallel to the *a*-plane at a height $x = 0{\cdot}375$ led to (*yz*) co-ordinates (0·075, 0·083) for the terminal nitrogen atom of the azide group. Further, three-dimensional Fourier lines and sections were then computed in order to refine these co-ordinates; during this process only a small number of those structure amplitudes towards which the strontium atoms contribute changed sign, but there was a general rearrangement in those for which the strontium contribution is zero. The final co-ordinates, derived from the Fourier section shown in Fig. 1 and the three-dimensional Fourier lines parallel to the [*a*] axis, are:

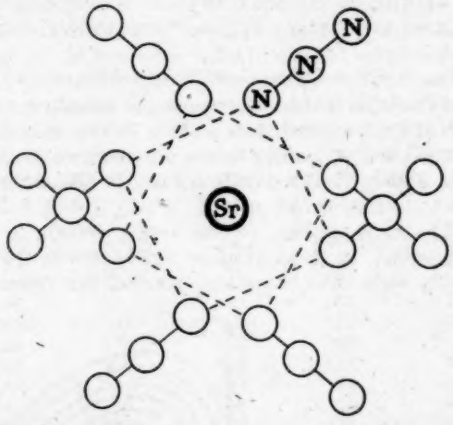
$$Sr\ \ 0\ \ 0\ \ 0 \qquad N_1\ \ 0{\cdot}383\ \ 0\ \ 0 \qquad N_2\ \ 0{\cdot}383\ \ 0{\cdot}058\ \ 0{\cdot}148$$

The agreement between the observed and the calculated structure amplitudes (the average descrepancy is 27%) is not of the same order as it is now customary to expect in structural determinations of organic substances; this may be attributed to the presence of the very heavy

strontium atom, which renders intensity measurements difficult; the contribution of the azide ion to the observed intensity is probably of the order of the experimental error for a high proportion of the planes.

Discussion of the Structure.—The equivalence of the two nitrogens at either end of the azide group—each is separated from the central nitrogen by 1·12 A.—shows that the structure is ionic. Fig. 2 represents the disposition of the nearest azide ions around any strontium ion. The

FIG. 2.



strontium ion has eight near neighbours; these can conveniently be classified in two sets of four. In the first set the strontium–nitrogen separation is 2·63 A., and in the second set 2·77 A. Each azide ion is disposed between four strontium ions, two at a distance of 2·77 A. and two at 2·63 A.

Experimental. Strontium carbonate (5 g.) was dissolved in 2% hydrazoic acid (30 ml.) and the solution concentrated on a water-bath; on cooling, a mass of extremely small crystals was deposited. Larger crystals suitable for *X*-ray photography were obtained from the mother-liquor by slow evaporation in an Erlenmeyer flask.

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THE UNIVERSITY, BIRMINGHAM 15. [*Received, September 9th*, 1946.]

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165. *The Crystal Structure of* p-*Dinitrobenzene.*

By F. J. LLEWELLYN.

The crystal structure of *p*-dinitrobenzene has been completely determined by utilising all the diffracted beams obtainable with Cu-$K\alpha$ *X*-radiation. The molecule is centrosymmetrical, and the carbon atoms of the benzene nucleus are located on a regular hexagon such that the C–C distance is 1·38$_5$ A. The nitro-group is planar, and coplanar with the rest of the molecule; its dimensions are C–N = 1·41, N–O = 1·23 A.

THE crystal structure of *p*-dinitrobenzene has been previously investigated by Hertel (*Z. physikal. Chem.*, 1930, **7**, *B*, 188), Bannerjee (*Phil. Mag.*, 1934, **18**, 1004), and James, King, and Horrocks (*Proc. Roy. Soc.*, 1935, **153**, *A*, 225); in the last investigation Mo-$K\alpha$ radiation was used to determine the intensities of the diffracted beams from the $\{h0l\}$, $\{hk0\}$, and $\{0kl\}$ planes—about 200 in all—the atomic parameters being determined by means of Fourier projections on the (*a*), (*b*), and (*c*) faces. The main features of the results are as follows: (i) The molecule of *p*-dinitrobenzene is centrosymmetrical; the benzene ring is not, however, a regular hexagon, as has previously been reported in other solid benzenoid substances, *e.g.*, benzene (Cox, *Proc. Roy. Soc.*, 1932, **135**, *A*, 491), hexamethylbenzene (Lonsdale, *ibid.*, 1929, **123**, *A*, 494). (ii) The nitro-group and the carbon of the benzene ring to which it is bonded are not coplanar. (iii) The two oxygen atoms of the nitro-group are not equidistant from the nitrogen atom.

The irregularity of the benzene ring and the non-equivalence of the two oxygen atoms of the nitro-group are not compatible with the usual conceptions of the function of resonance

which is to be expected in such a substance; various objections to, and criticisms of, these results have been made (see Pauling, "Nature of the Chemical Bond," p. 201). It seemed probable that, whilst the general arrangement of the molecules in the unit cell had been correctly determined, the detailed description of the molecule was inaccurate, mainly because the number of intensities used in computing the Fourier synthesis was insufficient, and also because of the considerable overlapping which occurs in projecting the structure on to both the *a*- and the *c*-planes.

It was decided, therefore, to repeat the structure determination, utilising all the {*hkl*} intensities obtainable with Cu-*K*α *X*-radiation—about 450 in all—and to ascertain the atomic co-ordinates by means of three-dimensional Fourier lines and sections.

Preliminary Crystallographic Data.—Small, well-defined, single crystals of *p*-dinitrobenzene were readily obtained by slow evaporation of an acetone solution; they exhibited the forms {110}, {100}, {101}, {011}, {111}; the symmetry appeared to be monoclinic holohedral and the habit was variable. *X*-Ray rotation and oscillation photographs confirmed the monoclinic symmetry and the axial dimensions previously reported by James *et al.* (*loc. cit.*), *viz.*, [*a*] = 11·05 A., [*b*] = 5·42 A., [*c*] = 5·65 A., β = 92° 18′; whence $a : b : c = 2{\cdot}039 : 1 : 0{\cdot}42$. Axial ratios quoted by Bodewig (*Ann. Physik*, 1876, **158**, 239) are $a : b : c = 2{\cdot}038 : 1 : 0{\cdot}43$, β = 92° 18′.

Various values for the density (g./c.c.) appear in the literature: 1·546 (Barker, *Z. Krist.*, 1908, **44**, 154), 1·625 (Lobry de Bruyn, *Rec. Trav. chim.*, 1894, **13**, 111), 1·623 (Brandl, quoted by Groth, "Chemische Kristallographie," **4**, 14), 1·64 (James *et al.*, *loc. cit.*); the density calculated from the *X*-ray data on the basis of two molecules in the unit cell is 1·64 (obs., by flotation, 1·63).

The only systematic halvings observed in the analysis of the *X*-ray oscillation photographs are {*h*0*l*} absent when $h + l \neq 2n$, and {0*k*0} absent when $k \neq 2n$. The space-group is therefore $P2_1/n(C_{2h}^5)$, which accommodates the four general positions ± (*x*, *y*, *z*) and ± ($x + \frac{1}{2}$, $\frac{1}{2} - y$, $\frac{1}{2} + z$) in each unit cell. Since there are only two molecules in the cell, it follows that these must be orientated about special two-fold positions, *i.e.*, each molecule is centrosymmetrical.

Measurement of Intensities.—In order to make the structure determination as accurate as possible, the intensities of the diffracted beams from all the {*hkl*} planes with spacings greater than 0·77 A. were determined photographically. Since photographic density is proportional to *X*-ray intensity only over a limited range (from 0 to 1·2 approximately) it was necessary to take a number of oscillation photographs covering the same range of crystal orientation in order that all the diffracted beams which occur should be recorded as photographic spots whose density was within the proportionality limits. Two methods were adopted: (*a*) to vary the exposure, in which case the whole photograph was either more or less dense in proportion to this variation, or (*b*) to maintain the exposure constant but to screen (with aluminium sheets of known absorbing power) those parts of the photographic film on which the more intense diffracted beams fell such that their photographic impression lay within the proportionality limits.

The latter method was finally adopted, since it permitted an easy correlation between the strongest and weakest spots on a given photograph and considerably reduced the number of photographs necessary with (*a*) to achieve the same end. The actual measurement was carried out visually by matching each of the spots on the photographic film, in turn, with one of a series of spots of known density on a previously prepared comparator. The standard series of spots on the comparator was obtained as follows. A piece of *X*-ray film was exposed to a suitably collimated *X*-ray beam for a short measured time such that on development a photographic image was just discernible; a second piece of film was then exposed to the same *X*-ray beam for this time, then moved to a new position and exposed again for a longer time, this operation being repeated with successive increases in exposure until the necessary range of density was covered. The film was developed under conditions exactly similar to those obtaining in the photography of the crystal. In order to facilitate the matching of the spots, those on the comparator were made to approximate in both size and shape to those produced on the oscillation photographs.

A set of intensities on an arbitrary scale was thus produced, and these were converted to an absolute scale by direct photometric comparison of the intensities of the orders of (100) with the (400) reflection from the ground cleavage face of rock-salt. The experimental structure amplitudes ($F_{obs.}$) derived from the observed intensities *Q* by the relation

$$Q = \frac{N^2 e^4 \lambda^3}{2m^2 c^4} \cdot \frac{1 + \cos^2 2\theta}{\sin 2\theta} \cdot F^2$$

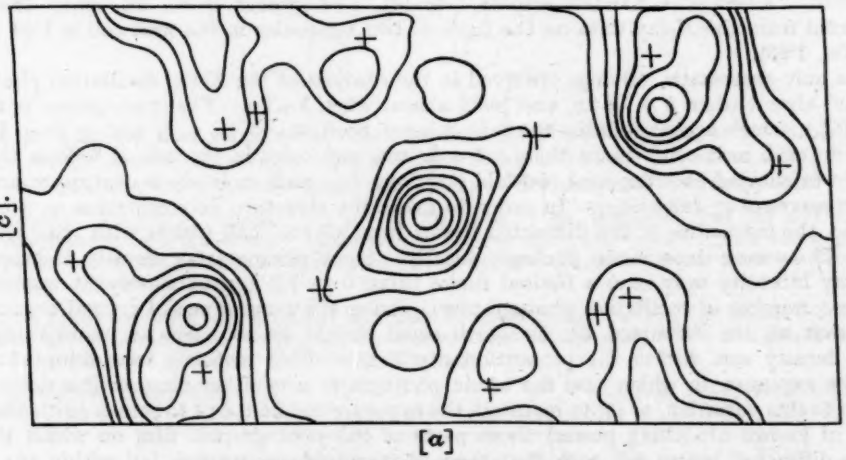
are listed in the table together with the calculated structure amplitudes ($F_{calc.}$) and the phase angles derived from the final atomic co-ordinates.

Determination of the Structure.—In order to define the structure it is necessary to determine the co-ordinates of six atoms, *viz.*, three carbons of the benzene ring, and one nitrogen and two oxygens of the nitro-group. The other half of the molecule is determinable by the operation of the centre of symmetry, and the second molecule by the operation of the glide plane. Since all the atoms in the structure are located in general positions, $\pm(x, y, z)$, $\pm(x + \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} + z)$, it is to be expected that a three-dimensional Harker–Patterson synthesis (*J. Chem. Physics*, 1936, **4**, 381) evaluated at $y = \frac{1}{2}$ would exhibit maxima in the Patterson function $P_{x\frac{1}{2}z}$, where

$$P_{x\frac{1}{2}z} = \sum_{H}\sum_{L} \cos 2\pi(hx + lz)\left(\sum_{K} F^2_{hkl} \cos 2\pi k/2\right)$$

at the points $\pm(\frac{1}{2} - 2x_r, \frac{1}{2} - 2z_r)$, (x_r, z_r) being the co-ordinates of an atom, and thus provide for the direct determination of the (xz) co-ordinates of all the atoms in the structure. Such a three-dimensional synthesis was evaluated, and the resulting contour map (Fig. 1) plotted over the whole unit cell; it is obvious that the maxima are too diffuse to be of any great service in determining accurate atomic co-ordinates.

FIG. 1.



Patterson–Harker Section at $y = \frac{1}{2}$.

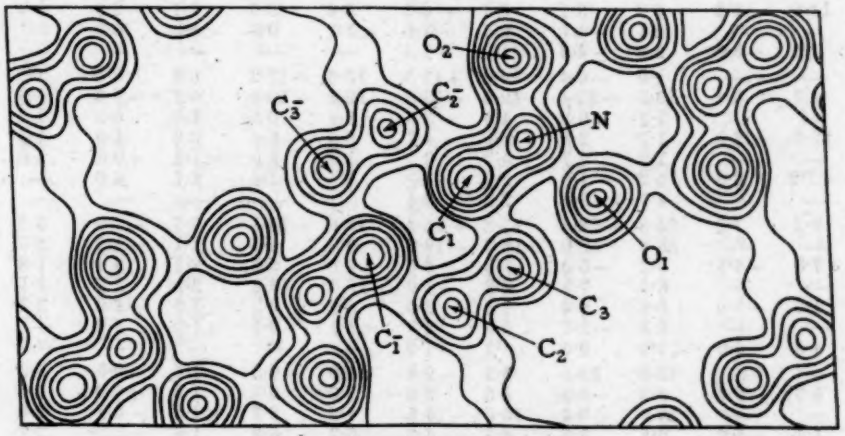
This result is in sharp contrast with that obtained in the determination of the structure of pentaerythritol (Llewellyn, Cox, and Goodwin, *J.*, 1937, 883) in which a Patterson–Harker three-dimensional summation gave rise to sharp maxima in the function P_{xy0} and permitted the accurate determination of the (xy) co-ordinates of the pentaerythritol molecule. It is interesting to compare the positions of the maxima $P_{x\frac{1}{2}z}$ as represented by the peaks in Fig. 1 with the positions (represented by crosses) of the maxima calculated from the final atomic co-ordinates. Although it may be allowed that there is qualitative coincidence, yet the value of the Patterson synthesis in determining even approximate atomic co-ordinates is practically negligible. This question is further discussed by Booth and Llewellyn (this vol., p. 839).

It became necessary therefore to postulate a molecule and a molecular orientation and to refine the resulting atomic co-ordinates in three stages: (i) by trial-and-error methods using the $\{h0l\}$ structure amplitudes to determine the x and z co-ordinates; (ii) to refine these co-ordinates by two-dimensional Fourier syntheses; (iii) to obtain approximate y co-ordinates from a consideration of the x and z co-ordinates determined in (ii) and the bond lengths postulated in the molecule, and to refine these (xyz) co-ordinates by three-dimensional Fourier sections and lines.

The model used in the first stages consisted of a regular hexagon for the benzene ring with carbon–carbon separations of 1·39 A., a planar $R{\cdot}NO_2$ group which was coplanar with the benzene ring with carbon–nitrogen separation of 1·47 A., and a nitrogen–oxygen separation of 1·23 A. This model was placed in the unit cell with the centre of the benzene ring coincident with the centre of symmetry (origin) and orientated by trial-and-error methods until approx-

imate agreement between the observed and calculated values of a few $\{h0l\}$ structure amplitudes was obtained. The (xz) co-ordinates were then refined by means of a number of two-dimensional Fourier projections involving all the $\{h0l\}$ amplitudes. The resulting contour map is shown in Fig. 2.

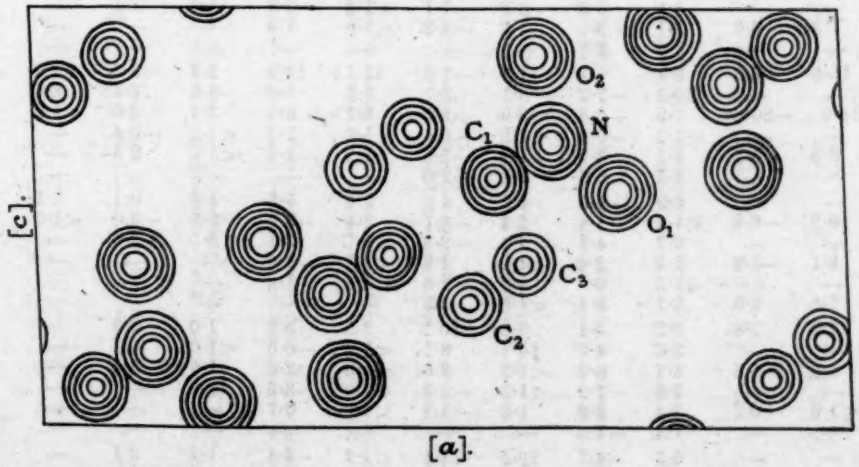
FIG. 2.



Fourier Projection on to 010.

These co-ordinates were then used in conjunction with the model to calculate approximate y co-ordinates. With these (xyz) co-ordinates the phase angles of all the $\{hkl\}$ structure amplitudes were calculated, and then the co-ordinates refined by successive three-dimensional Fourier lines parallel to [010] at the xy co-ordinates of each atom in turn and by three-dimensional Fourier sections parallel to (010) at the y co-ordinates of each of the atoms. After two such complete cycles of operations the agreement between the calculated and the observed structure amplitudes became satisfactory; a third set of syntheses resulted in no alteration of the phase angles. The various Fourier sections are illustrated in a composite drawing in Fig. 3.

FIG. 3.



The final atomic co-ordinates are:

Atom.	x.	y.	z.	Atom.	x.	y.	z.
C_1	0·070	0·192	0·090	N	0·142	0·387	0·184
C_2	0·032	−0·117	−0·206	O_1	0·220	0·472	0·057
C_3	0·102	0·075	−0·115	O_2	0·124	0·460	0·385

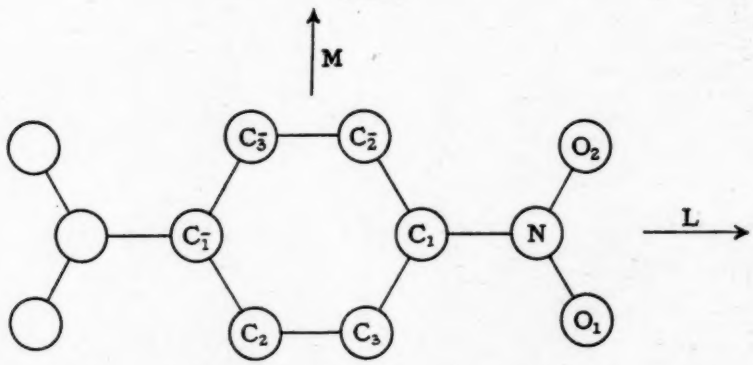
The average discrepancy between observed and calculated structure factors is 24%.

k =	0.		1.		2.		3.		4.		5.	
hl.	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$
00	172·0	—	—	—	25·1	+27·2	—	—	4·1	−3·0	—	—
01	—	—	7·6	+8·2	8·5	+9·0	7·8	−6·0	9·6	+11·5	<1·2	0·5
02	2·5	+1·6	9·6	−10·6	3·9	+7·8	4·1	+3·0	7·7	+9·8	5·4	5·0
03	—	—	12·3	−10·1	7·2	7·4	4·9	−4·5	9·9	10·4	1·4	−1·7
04	14·0	−12·2	1·9	3·1	3·4	−4·5	5·6	6·6	<1·1	−2·0	<0·9	−2·7
05	—	—	4·1	−6·1	2·5	−3·1	<1·1	0·5	<1·0	0·3	—	—
06	2·8	−3·0	2·9	−4·6	<1·0	−1·5	—	—	—	—	—	—
10	—	—	1·9	−0·4	14·0	+12·5	15·6	−13·2	8·8	8·5	1·0	−0·5
11	1·7	0·8	23·8	−30·4	12·9	−13·6	12·4	−10·9	5·2	−4·5	1·5	0·8
12	—	—	7·2	6·8	4·5	−3·6	3·4	−0·5	7·6	6·8	1·7	−2·6
13	22·9	−22·0	1·7	2·8	4·9	−4·7	6·0	+6·4	2·6	1·0	1·4	−4·0
14	—	—	1·9	3·7	4·7	0	7·3	8·0	<1·2	+0·6	1·6	+2·7
15	<1·2	0·6	4·2	−1·0	2·8	0·9	1·6	−1·4	2·1	4·0	—	—
16	—	—	4·7	3·4	2·3	0·4	—	—	—	—	—	—
20	9·3	7·2	25·8	−28·6	17·8	−16·4	18·6	−16·1	7·7	−7·0	3·3	−5·2
21	—	—	38·3	52·0	16·3	−19·6	6·8	4·4	1·1	−1·5	2·9	−2·9
22	7·3	−4·4	6·2	−5·6	5·3	6·0	4·6	5·3	2·1	3·4	1·8	1·7
23	—	—	6·4	7·5	3·2	−1·9	12·4	13·2	2·9	2·7	1·1	2·0
24	1·6	−1·0	6·2	6·4	1·5	3·5	8·3	9·5	3·9	−2·0	3·1	4·7
25	—	—	3·3	−2·4	5·7	5·7	<1·1	−0·7	<1·0	1·4	—	—
26	4·3	−6·0	<1·1	0·5	1·1	−1·9	—	—	—	—	—	—
30	—	—	35·6	32·4	3·8	−2·4	<1·0	−0·5	1·4	0·9	1·5	−0·5
31	5·3	−2·4	9·6	−8·2	1·5	3·2	7·6	6·7	1·6	+0·2	4·5	5·4
32	—	—	10·9	−8·4	15·5	−13·6	1·8	2·7	<1·2	−0·1	2·9	−2·4
33	1·4	−3·0	3·8	3·0	4·8	4·4	5·2	5·8	1·6	−2·0	2·7	1·6
34	—	—	10·0	−9·9	9·3	6·6	<1·2	1·7	<1·1	−0·7	—	—
35	<1·2	1·9	1·8	0·9	2·6	2·9	<1·1	1·1	—	—	—	—
36	—	—	<1·0	−0·5	<0·9	−0·9	—	—	—	—	—	—
40	23·9	−18·0	1·7	−2·4	7·3	−5·9	8·3	7·1	2·5	2·4	<1·0	−0·1
41	—	—	18·0	−20·0	21·5	−25·4	8·0	−9·5	4·3	−5·3	4·7	−5·6
42	12·3	14·0	10·7	−9·2	11·8	13·0	9·8	−8·4	<1·2	0·3	2·3	−3·3
43	—	—	6·8	−7·5	<1·1	1·4	6·8	6·2	1·7	−1·7	<1·0	−0·8
44	5·2	9·4	2·5	1·7	8·3	11·0	<1·2	2·6	2·2	3·7	—	—
45	—	—	5·3	6·9	5·3	4·4	<1·2	−1·0	—	—	—	—
46	2·0	3·0	2·1	3·1	—	—	—	—	—	—	—	—
50	—	—	5·2	−4·4	7·0	−6·6	2·6	−2·4	2·9	1·3	2·3	−1·8
51	21·3	20·6	6·0	−5·7	15·9	13·2	4·0	−3·7	1·0	−1·5	2·2	−3·9
52	—	—	6·9	−3·2	2·7	−1·8	8·8	8·8	<1·2	1·8	<1·1	2·5
53	8·5	−5·4	2·7	−2·5	2·2	3·3	6·6	−6·5	<1·2	2·1	<1·0	−0·7
54	—	—	4·1	5·5	8·2	7·1	<1·2	0·8	<1·0	1·1	—	—
55	1·2	−3·0	2·1	5·0	1·6	−4·3	<1·0	1·9	—	—	—	—
56	—	—	2·0	2·2	—	—	—	—	—	—	—	—
60	10·5	−8·2	9·4	7·1	1·7	−1·2	11·7	10·9	3·4	−3·7	<1·0	−0·1
61	—	—	10·9	−7·2	5·7	3·7	3·7	4·0	3·8	4·4	1·1	2·8
62	24·0	−20·0	7·9	−6·8	8·9	−9·6	8·7	−9·0	2·1	−4·0	<1·0	0·3
63	—	—	<1·2	−0·4	<1·2	−0·4	1·2	2·3	<1·2	−0·4	—	—
64	6·8	−8·4	4·1	4·3	1·9	−3·5	1·2	−2·0	<1·0	0·3	—	—
65	—	—	5·3	6·6	1·1	−2·6	—	—	—	—	—	—
70	—	—	6·9	−5·0	4·2	4·8	7·4	5·9	1·0	0·1	1·1	1·2
71	6·2	−6·4	<1·2	−1·4	2·3	−3·1	2·4	−3·0	3·5	−5·0	<1·0	0·6
72	—	—	6·7	4·1	2·4	−2·8	3·7	3·1	5·0	−5·6	—	—
73	8·1	−5·6	2·8	2·4	<1·2	1·6	<1·1	−1·6	—	—	—	—
74	—	—	<1·2	0	1·7	−1·8	<1·1	1·4	—	—	—	—
75	7·5	8·0	2·7	3·4	<1·0	2·3	—	—	—	—	—	—
80	7·2	7·8	5·2	4·1	9·2	10·2	3·5	4·0	1·0	−0·3	—	—
81	—	—	3·6	4·0	10·1	8·1	<1·2	−0·5	<1·0	0·7	—	—
82	4·8	−1·6	4·2	3·0	<1·2	2·6	<1·2	2·0	1·9	5·5	—	—
83	—	—	7·8	−7·2	<1·2	−1·7	<1·0	−3·6	—	—	—	—
84	<1·0	0·2	2·4	3·0	1·9	−1·1	<1·0	0·7	—	—	—	—
85	—	—	1·3	−4·6	—	—	—	—	—	—	—	—
90	—	—	6·5	−4·7	10·5	11·1	<1·2	−2·4	1·7	2·1	—	—
91	1·8	−1·0	5·6	4·5	<1·2	1·1	<1·2	0·7	1·0	0·5	—	—
92	—	—	2·1	−4·0	<1·2	−0·9	3·4	−6·2	1·2	−0·5	—	
93	<1·0	1·3	1·4	1·3	<1·2	−0·5	<1·0	0	—	—	—	
94	—	—	2·5	−3·1	<1·0	1·7	—	—	—	—	—	—
10·0	1·7	−0·8	1·8	1·3	3·1	2·4	3·3	−4·5	—	—	—	—
10·1	—	—	8·5	8·0	2·7	1·8	<1·0	−0·3	—	—	—	—
10·2	7·7	7·0	3·9	1·6	<1·2	0·8	<1·0	0·2	—	—	—	—
10·3	—	—	1·8	0·2	<1·0	1·4	—	—	—	—	—	—
10·4	<1·0	2·0	—	—	—	—	—	—	—	—	—	—

$h =$	0.		1.		2.		3.		4.		5.	
hl.	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$
11·0	—	—	6·1	7·5	1·9	3·0	0·7	3·9	—	—	—	—
11·1	3·1	1·9	6·2	5·4	1·1	−1·6	1·0	0·5	—	—	—	—
11·2	—	—	2·2	3·1	<1·0	0	—	—	—	—	—	—
11·3	1·5	−0·9	<1·0	−0·9	—	—	—	—	—	—	—	—
12·0	3·4	−5·8	3·6	4·3	2·6	−4·0	—	—	—	—	—	—
12·1	—	—	<1·0	3·1	—	—	—	—	—	—	—	—
12·2	7·2	8·1	—	—	—	—	—	—	—	—	—	—
1$\bar{1}$	32·7	−48·8	9·6	11·8	5·1	1·6	1·3	1·5	2·3	−2·4	3·8	−3·1
1$\bar{2}$	—	—	13·5	−10·6	0·7	−2·4	3·1	−1·0	1·3	−1·5	5·2	4·2
1$\bar{3}$	5·9	3·0	8·2	2·9	9·1	8·8	<1·1	−4·0	5·5	10·8	<1·0	−0·8
1$\bar{4}$	—	—	3·1	−0·4	2·9	2·4	2·9	−4·1	<1·0	−2·5	2·6	−2·8
1$\bar{5}$	3·6	5·0	1·4	+0·2	1·9	5·1	1·3	1·3	1·3	+2·0	—	—
1$\bar{6}$	—	—	2·7	−6·6	2·4	2·3	—	—	—	—	—	—
2$\bar{1}$	—	—	12·8	−9·0	6·0	5·2	1·1	−1·9	1·4	−2·6	7·8	6·9
2$\bar{2}$	21·0	−19·6	2·0	0·4	20·4	−20·0	4·1	−3·8	3·0	−2·8	5·1	−4·2
2$\bar{3}$	—	—	12·0	−11·1	3·8	−3·0	5·7	−5·1	<1·2	0·9	3·1	2·4
2$\bar{4}$	3·2	−4·0	5·4	5·4	4·4	−3·7	<1·2	0·9	<1·1	1·5	<1·0	1·4
2$\bar{5}$	—	—	4·0	2·8	9·5	11·4	<1·1	−1·6	1·8	4·1	—	—
2$\bar{6}$	2·5	6·0	3·8	2·0	3·2	7·2	—	—	—	—	—	—
3$\bar{1}$	5·2	4·4	7·2	−8·6	8·2	−5·0	1·6	1·1	<3·2	2·5	1·4	0·9
3$\bar{2}$	—	—	4·9	2·6	<1·0	−0·2	9·5	10·6	<3·2	−1·9	11·1	10·8
3$\bar{3}$	1·5	−0·8	3·1	1·4	10·1	−6·5	<1·2	−1·0	4·1	−3·0	1·1	−1·3
3$\bar{4}$	—	—	7·7	8·2	2·5	−1·3	3·2	−2·5	1·9	−1·6	—	—
3$\bar{5}$	1·7	−5·2	4·3	4·3	1·9	−3·9	<1·1	−0·3	—	—	—	—
3$\bar{6}$	—	—	2·4	−0·5	3·6	6·4	—	—	—	—	—	—
4$\bar{1}$	—	—	19·8	−17·9	7·9	8·9	9·6	−9·6	5·6	4·4	1·1	0
4$\bar{2}$	4·0	−3·6	6·4	−2·8	8·2	−6·0	5·9	6·8	2·0	3·7	5·9	8·3
4$\bar{3}$	—	—	5·4	2·9	<1·1	−0·8	2·9	3·1	2·1	1·4	4·9	5·7
4$\bar{4}$	13·8	15·6	6·5	6·4	1·5	1·2	1·2	5·3	3·1	−2·7	—	—
4$\bar{5}$	—	—	9·4	11·6	1·9	1·0	<1·1	1·8	—	—	—	—
4$\bar{6}$	2·5	−3·1	1·7	3·4	—	—	—	—	—	—	—	—
5$\bar{1}$	9·6	−8·8	6·2	−2·4	5·8	3·8	3·9	5·0	8·9	9·7	1·4	−2·6
5$\bar{2}$	—	—	15·4	14·8	1·2	1·2	8·8	−10·5	4·8	3·5	<1·0	−1·8
5$\bar{3}$	12·5	10·6	9·8	−5·9	<1·1	−1·0	1·2	−0·9	<1·2	−1·9	<1·0	4·6
5$\bar{4}$	—	—	1·2	−3·5	<1·2	−0·4	<1·2	−2·2	<1·1	−0·3	—	—
5$\bar{5}$	7·3	7·0	5·1	6·0	<1·8	0·1	<1·1	1·8	—	—	—	—
5$\bar{6}$	—	—	1·0	2·6	—	—	—	—	—	—	—	—
6$\bar{1}$	—	—	3·2	5·0	2·3	4·8	3·6	5·8	7·7	9·7	<1·1	−1·5
6$\bar{2}$	3·1	1·8	7·8	−7·0	8·5	7·2	<1·2	0·4	7·6	7·1	1·8	1·4
6$\bar{3}$	—	—	8·6	8·2	<1·2	−0·2	<1·2	−1·8	<1·2	3·5	—	—
6$\bar{4}$	18·3	18·7	5·4	−4·3	2·7	3·1	1·2	− 5·0	<1·0	−2·1	—	—
6$\bar{5}$	—	—	2·1	−4·0	<1·1	−4·1	—	—	—	—	—	—
7$\bar{1}$	21·5	−19·2	4·6	5·2	6·9	−7·0	7·6	8·9	1·8	−3·7	1·0	2·5
7$\bar{2}$	—	—	5·2	5·2	8·2	−4·5	2·0	2·4	2·4	5·0	1·1	−1·3
7$\bar{3}$	<1·2	−1·6	7·1	−7·2	1·2	−3·0	<1·2	−1·6	<1·1	0·7	—	—
7$\bar{4}$	—	—	7·9	7·1	1·2	3·0	<1·1	−0·4	—	—	—	—
7$\bar{5}$	4·4	7·8	<1·2	−1·4	1·0	1·5	—	—	—	—	—	—
8$\bar{1}$	—	—	1·0	1·5	2·7	−3·0	8·4	10·0	1·2	−2·2	—	—
8$\bar{2}$	1·9	−2·2	2·4	−2·7	2·3	2·0	<1·2	0·4	<1·2	−0·5	—	—
8$\bar{3}$	—	—	6·8	6·1	10·3	−9·0	<1·2	−1·2	<1·1	−3·1	—	—
8$\bar{4}$	3·7	−5·7	4·0	−3·5	4·9	−6·7	<1·1	−1·6	—	—	—	—
8$\bar{5}$	—	—	<1·0	−0·9	—	—	—	—	—	—	—	—
9$\bar{1}$	3·1	4·0	<1·2	0·6	7·0	10·0	1·1	1·8	<1·1	1·4	—	—
9$\bar{2}$	—	—	2·3	−2·8	6·3	−6·1	4·4	4·1	<1·0	−0·7	—	—
9$\bar{3}$	3·9	5·1	4·4	−1·7	3·7	5·4	1·1	1·4	—	—	—	—
9$\bar{4}$	—	—	1·8	4·9	2·3	−3·3	—	—	—	—	—	—
10$\bar{1}$	—	—	5·1	−5·9	1·8	2·2	1·4	0·9	—	—	—	—
10$\bar{2}$	<1·1	−0·3	4·4	−2·9	1·9	1·9	5·6	−4·8	—	—	—	—
10$\bar{3}$	—	—	1·7	−6·6	3·1	−4·1	1·0	−2·5	—	—	—	—
10$\bar{4}$	1·9	−0·2	—	—	—	—	—	—	—	—	—	—
11$\bar{1}$	5·2	−3·6	1·2	−1·6	1·2	1·8	3·7	−5·4	—	—	—	—
11$\bar{2}$	—	—	2·0	1·1	<1·2	0·8	—	—	—	—	—	—
11$\bar{3}$	1·0	1·3	1·0	−2·8	—	—	—	—	—	—	—	—
12$\bar{1}$	—	—	1·3	−0·1	1·2	1·1	—	—	—	—	—	—
12$\bar{2}$	4·9	−6·4	<1·0	1·1	—	—	—	—	—	—	—	—

Description of the Structure.—A diagrammatic representation of the *p*-dinitrobenzene molecule is shown in Fig. 4. The atoms C_1, $C_{\bar{1}}$, etc., are obtained by inversion of the atoms C_1, C_2, etc., across the centre of symmetry coincident with the centre of the molecule. Within the limits of experimental error all the atoms lie in a plane which is so orientated within the

FIG. 4.



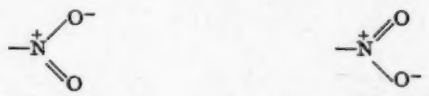
unit cell that the molecular axes, *L* and *M*, make angles of 48° 42′ and 5° 42′ respectively with the plane 010. Bond angles and bond lengths calculated from the measured atomic co-ordinates and cell dimensions are as follows :

C_1–$C_{\bar{2}} = 1{\cdot}38_5$ A.	C_1–N = 1·41 A.	$<O_1$–N–$O_2 = 124°$
C_2–$C_{\bar{3}} = 1{\cdot}38_5$ A.	N–O_1 = 1·23 A.	$<O_1$–N–$C_1 = 117\frac{1}{2}°$
C_3–$C_1 = 1{\cdot}38_5$ A.	N–O_2 = 1·23 A.	$<O_2$–N–$C_1 = 118\frac{1}{2}°$

Other distances within the molecule are : O_1–O_2 = 2·17; C_1–O_1 = 2·25; C_1–O_2 = 2·25 A. The error in the bond lengths is probably not more than ± 0·02 A., and the angles are probably accurate to within ± 2°.

The anomalies in the bond lengths and bond angles reported by James (*loc. cit.*) are not substantiated by the present investigation. The benzene ring is a regular hexagon, and in this respect falls into line with the results of earlier structural work on benzenoid substances.

The two oxygen atoms of the nitro-group are equidistant at 1·23 A. from the nitrogen atom. This result is in agreement with the resonance mechanism suggested by Pauling in which the two principal forms are :



The observed distance, 1·23 A., is greater than the calculated value of 1·19 A. and agrees more nearly with the value of 1·21 ± 0·02 found in nitromethane. The ONO bond angle is 124° as compared with 127° found in nitromethane and the theoretical value of 125° 16′.

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THE UNIVERSITY, BIRMINGHAM 15. [*Received, September 9th*, 1946.]

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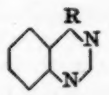
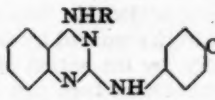
166. *Synthetic Antimalarials. Part XVI. 4-Dialkylaminoalkylamino-quinazolines. Variation of Substituents in the 6- and 7-Positions.*

By NORMAN B. CHAPMAN, GEOFFREY M. GIBSON, and FREDERICK G. MANN.

A series of seven quinazolines having different dialkylaminoalkylamino-groups in the 4-position has been prepared. Series of 4-dialkylaminoalkylaminoquinazolines, having in addition the 6-chloro-, 7-chloro-, 7-nitro-, 6-methoxy-, and 7-methoxy-substituents, have also been synthesised. This wide range of quinazolines has been tested for antimalarial activity and some noteworthy variations have been revealed.

THIS investigation originated in the observation made in the laboratories of Imperial Chemical Industries Ltd. that 4-γ-diethylaminopropylaminoquinazoline (I; R = NH·[CH$_2$]$_3$·NEt$_2$) showed activity against *P. gallinaceum* in chicks. This result was apparently at variance with those of Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, **8**, 1797) who first prepared this compound, its 6-chloro-derivative, and several other 6-substituted 4-dialkylaminoalkylaminoquinazolines and reported that they possessed no antimalarial activity. It appeared that the apparent discrepancy might possibly be due to a species specificity which these quinazoline derivatives might show in their antimalarial action, the Russian workers having probably tested the compounds against *P. præcox* (cf. Magidson *et al.*, *J. Microbiol. and Immunobiol.*, 1934, **13**, 685; *Trop. Dis. Bull.*, 1935, **32**, 419).

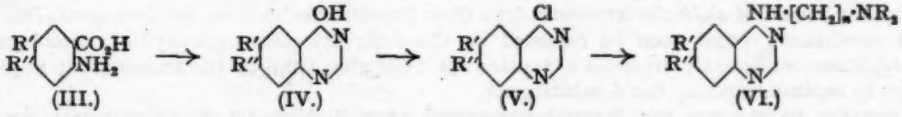
In view of the fact that 2-*p*-chloroanilino-4-dialkylaminoalkylaminoquinazolines of type (II; R = dialkylaminoalkyl) had also been shown to possess marked antimalarial activity against *P. gallinaceum* in chicks (Curd, Landquist, and Rose, Part XIV, this vol., p. 775) it became desirable to make a systematic study of the relationship between structure and antimalarial activity in 4-dialkylaminoalkylaminoquinazolines of type (I). Accordingly, we first prepared a series of compounds of type (I) having no substituent in the benzene ring, but

(I.)  (II.) 

having in turn seven different dialkylaminoalkylamino-groups in the 4-position. We then prepared five similar series of compounds having in turn the 6-chloro-, 7-chloro-, 7-nitro-, 6-methoxy-, and 7-methoxy-substituents. Our choice both of these groups and their position was determined largely by the presence of the same groups in analogous positions in various quinoline and acridine compounds of known antimalarial activity. Thus, for instance, Magidson and Rubtsov (*J. Gen. Chem. Russia*, 1937, **7**, 1896) and Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) have reported on the antimalarial activity of 4-dialkylaminoalkylamino-6-methoxyquinolines, and D.R.-P. 683,692 relates *inter alia* to 7-halogeno-4-dialkylaminoalkylaminoquinolines which are stated to possess antimalarial activity. 7-Nitro-4-β-diethylaminoethylamino-3-ethoxyacridine (Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396) is an example of an active antimalarial containing a nitro-group.

Over forty 4-dialkylaminoalkylaminoquinazolines have thus been prepared. In addition, some of the 4-hydroxyquinazoline derivatives utilised as intermediates in the synthesis of these quinazolines (*vide infra*) have also been submitted for test for prophylactic action because they were seen to be distantly related to Endochin (4-hydroxy-7-methoxy-3-*n*-heptylquinaldine) (C.I.O.S. Reports Nos. XXIII, 12, 13; XXIV, 20; XXV, 54, H.M. Stationery Office; see also Fitch, *Pharm. J.*, 1945, 182) which is stated to possess prophylactic activity against avian malaria.

The general route employed for the preparation of all these quinazolines consisted first in heating the appropriate anthranilic acid (or ester) (III) with formamide to obtain the



(III.) (IV.) (V.) (VI.)

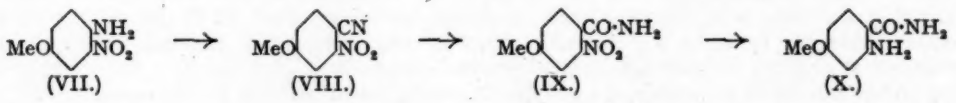
corresponding 4-hydroxyquinazoline (IV), which when suitably treated with a mixture of phosphorus pentachloride and phosphorus oxychloride gave the 4-chloroquinazoline (V). This when boiled in alcoholic solution with the dialkylaminoalkylamine furnished the 4-dialkylaminoalkylaminoquinazoline (VI), which was isolated either as the free base or directly as the hydrochloride.

The various substituted anthranilic acids and quinazoline intermediates were prepared as follows. Direct chlorination of methyl anthranilate (Freundler, *Bull. Soc. chim.*, 1911, **9**, 606) gave methyl 5-chloroanthranilate (as III; R′ = Cl, R″ = H) which readily condensed with formamide to give 6-chloro-4-hydroxyquinazoline (IV; R′ = Cl, R″ = H) and thence 4 : 6-dichloroquinazoline (V; R′ = Cl, R″ = H) (cf. Magidson *et al.*, *loc. cit.*). 4-Chloroanthranilic acid (III; R′ = H, R″ = Cl) was prepared by a modification (Curd *et al.*, forthcoming communication) of Cohn's method (*Monatsh.*, 1901, **22**, 485), 4-chloroaceto-*o*-toluidide being oxidised to 4-chloroacetylanthranilic acid, and then hydrolysed in turn to

4-chloroanthranilic acid. This acid furnished *7-chloro-4-hydroxyquinazoline* (IV; R′ = H, R″ = Cl) and 4 : 7-*dichloroquinazoline* (V; R′ = H, R″ = Cl). 4-Nitroanthranilic acid (III; R′ = H, R″ = NO_2), similarly prepared from 4-nitroaceto-*o*-toluidide, furnished 7-nitro-4-hydroxy- and *4-chloro-7-nitro-quinazolines* (IV and V; R′ = H, R″ = NO_2).

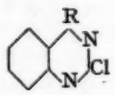
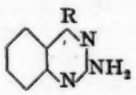
5-Methoxyanthranilic acid (III; R′ = OMe, R″ = H) was prepared by oxidising 2-nitro-5-methoxybenzaldehyde (Mason, *J.*, 1925, 1195) to 2-nitro-5-methoxybenzoic acid and reducing the latter. This acid gave *4-hydroxy-6-methoxy-* and *4-chloro-6-methoxy-quinazoline* (IV and V; R′ = OMe, R″ = H).

4-Methoxyanthranilamide (X) was prepared by converting 2-nitro-4-methoxyaniline (VII) into 2-nitro-4-methoxyphenyl cyanide (VIII) (cf., Cook, Heilbron, Reed, and Strachan, *J.*, 1945, 861), which on short treatment with sulphuric acid yielded *2-nitro-4-methoxybenzamide*



(VII.) (VIII.) (IX.) (X.)

(IX): reduction with ferrous hydroxide then gave (X). *4-Hydroxy-7-methoxyquinazoline* (IV; R′ = H, R″ = OMe) was readily prepared by the action of formic acid on this amide: it was also prepared, but less effectively, by the action of formamide on 4-methoxyanthranilic acid or its methyl ester. The usual treatment then furnished *4-chloro-7-methoxyquinazoline* (V; R′ = H, R″ = OMe).

(XI.)   (XII.)

In addition to the above quinazolines in which substituents in the pyrimidine ring were limited to the 4-position, the preparation of 2-amino-4-dialkylaminoalkylaminoquinazolines has been investigated, since Hull, Lovell, Openshaw, Payman, and Todd (Part III, *J.*, 1946, 357) have reported that the corresponding 2-amino-4-dialkylaminoalkylamino-5 : 6-dimethylpyrimidines possessed antiplasmodial activity. For this purpose 2-chloro-4-β-diethylaminoethylaminoquinazoline (XI; R = NH·$[CH_2]_2$·NEt_2) was heated with alcoholic ammonia to give *2-amino-4-β-diethylaminoethylaminoquinazoline* (XII; R = NH·$[CH_2]_2$·NEt_2), but the yield, which was never high, was markedly decreased by even small changes in the time and temperature of heating. 2-Chloro-4-β-diethylaminoethylaminoquinazoline (cf. Part XIV, *loc. cit.*) was very conveniently prepared by boiling 2 : 4-dichloroquinazoline (Lange, Roush, and Asbeck, *J. Amer. Chem. Soc.*, 1930, **52**, 3698) in alcoholic solution with one equivalent of β-diethylaminoethylamine. 2-Chloro-4-δ-diethylamino-α-methylbutylaminoquinazoline (XI; R = NH·CHMe·$[CH_2]_3$·NEt_2) was similarly prepared, but this compound could not be satisfactorily converted into the 2-amino-derivative by the action of either alcoholic ammonia or potassium phthalimide. Many attempts were also made to convert 2-chloro-4-methylthioquinazoline (XI; R = SMe) (Part XIV) and 2-chloro-4-phenoxyquinazoline (Lange *et al.*, *loc. cit.*) by the action of alcoholic ammonia into their 2-amino-derivatives, in the expectation that the 4-substituent might then be replaced by the δ-diethylamino-α-methylbutylamino-group, but conditions sufficiently vigorous to replace the 2-chlorine atom by the amino-group appeared always to replace similarly the 4-substituent.

Attempts to prepare the 2-amino-compound from *2-chloro-4-β-diethylaminoethylamino-7-methoxyquinazoline* also failed. This compound, although first prepared in the laboratories of Imperial Chemical Industries Ltd., has not yet been reported and is therefore described in this paper. Its synthesis involved the preparation of 2 : 4-*dihydroxy-7-methoxyquinazoline* from *2-carbamido-4-methoxybenzoic acid*, followed by conversion into 2 : 4-*dichloro-7-methoxyquinazoline* and condensation with β-diethylaminoethylamine.

The antimalarial activity (against the blood invasive forms of *P. gallinaceum*) of all the above 4-dialkylaminoalkylaminoquinazolines has been estimated by tests in chicks, by the method described by Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139). The results are summarised in Table I where the usual method of expressing antimalarial activity is employed. For the antimalarial tests, certain of the 4-substituted quinazolines were weighed as free base (anhydrous or hydrated) which was then solubilised with dilute lactic acid: others were weighed as hydrochlorides or sulphates. The particular compound (base or salt) is accordingly indicated in column 4.

TABLE I.

Antimalarial Activity of 4-Substituted Quinazolines.

Ref. No.	Substituent: 6- or 7-position.	Substituent: 4-position.	Weighed as	Dose, mg./kg.	Activity.
5022	—	NH·[CH$_2$]$_3$·NEt$_2$	base	40	—
5023	—	NH·[CH$_2$]$_3$·NMe$_2$	,,	80	++
				60	+
				40	—
3623 *	—	NH·[CH$_2$]$_3$·NEt$_2$	,,	120	++
				40	—
5064	—	NH·[CH$_2$]$_3$·NHBu^a	,,	160	±
				80	—
5024	—	NH·[CH$_2$]$_3$·NBu$^a_2$	,,	40	—
5021	—	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	,,	60	++
				40	+
5026	—	NH·[CH$_2$]$_2$·O·[CH$_2$]$_2$·NEt$_2$	,,	80	—
5025	—	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	monohydrate	80	
5683	6-Cl	OH	base	20	—
5684	,,	NH·[CH$_2$]$_2$·NEt$_2$	monohydrochloride	160	—
				80	—
				40	—
5688	,,	NH·[CH$_2$]$_3$·NMe$_2$	,,	160	+
				80	±
5685	,,	NH·[CH$_2$]$_3$·NEt$_2$	,,	160	±
				80	—
5689	,,	NH·[CH$_2$]$_3$·NBu$^a_2$	,,	160	—
5687	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	base	80	+ to ++
				40	
5686	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	monohydrochloride	160	—
5245	7-Cl	NH·[CH$_2$]$_2$·NEt$_2$	base	80	+ to ++
				40	—
5248	,,	NH·[CH$_2$]$_3$·NMe$_2$	,,	80	++
				40	+ to ++
				20	—
5247	,,	NH·[CH$_2$]$_3$·NEt$_2$	,,	80	++
				40	+
				20	±
5249	,,	NH·[CH$_2$]$_3$·NBu$^a_2$	,,	160	++
				80	+
				40	—
5246	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	,,	20	++
				10	—
5251	,,	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	,,	80	++
				40	+
				20	±
5250	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	hemihydrate	160	++
				80	+
5682	7-NO$_2$	OH	base	not tested	
5407	,,	NH·[CH$_2$]$_2$·NEt$_2$	monohydrochloride	320	+ to ++
				160	—
5409	,,	NH·[CH$_2$]$_3$·NMe$_2$	,,	160	—
5408	,,	NH·[CH$_2$]$_3$·NEt$_2$	,,	160	—
5410	,,	NH·[CH$_2$]$_3$·NBu$^a_2$	,,	160	±
				80	—
5406	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	,,	320	++
				160	+ to ++
				80	—
5412	,,	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	,,	160	—
5411	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	,,	160	—
6123	6-OMe	OH	base	80	—
6117	,,	NH·[CH$_2$]$_2$·NEt$_2$	disulphate	140	—
6121	,,	NH·[CH$_2$]$_3$·NMe$_2$	base	80	+ to ++
6118	,,	NH·[CH$_2$]$_3$·NEt$_2$	disulphate	140	+
6122	,,	NH·[CH$_2$]$_3$·NBu$^a_2$	,,	120	—
6120	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	monohydrate	80	++
6119	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	base	80	+
5681	7-OMe	OH	,,	not tested	
5252	,,	NH·[CH$_2$]$_2$·NEt$_2$	,,	160	++
				80	+

* Prepared by Dr. J. K. Landquist, Imperial Chemical Industries Ltd. (Dyestuffs Division).

TABLE I—*contd.*

Ref. No.	Substituent: 6- or 7-position.	Substituent: 4-position.	Weighed as	Dose, mg./kg.	Activity.
5256	7-OMe	$NH\cdot[CH_2]_3\cdot NMe_2$	base	80	++
				40	—
5253	,,	$NH\cdot[CH_2]_3\cdot NEt_2$	disulphate	160	+ to ++
				80	—
5257	,,	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	,,	160	+
				80	—
5255	,,	$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$	base	40	++
				20	+
5258	,,	$NH\cdot[CH_2]_3\cdot O\cdot[CH_2]_2\cdot NEt_2$	monohydrate	160	++
				80	±
5254	,,	$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	base	80	++
				40	+
5622	2-amino-4-β-diethylaminoethylamino-quinazoline		,,	40	++
				20	+

The following 4-hydroxyquinazolines were tested for prophylactic activity against *P. gallinaceum* in chicks by the method described by Davey (*Ann. Trop. Med. Parasit.*, 1945, **40**, in the press) but found to be inactive: 5681 and 5682 at 4 mg./50 g., and 5683 at 1 mg./50 g. In addition, 5622 was found to be inactive prophylactically at 8 mg./50 g., and 5246, which showed the highest activity against the blood forms of *P. gallinaceum* of all the 4-dialkylaminoalkylaminoquinazolines investigated, likewise showed no prophylactic activity (at 4 mg./50 g.).

Although the detailed biological results, summarised in Table I, will be published and discussed elsewhere, it may be noted that, in each of the six series of 4-dialkylaminoalkylaminoquinazolines investigated, highest activity was found in the compound containing the δ-diethylamino-α-methylbutylamino-side chain and that substitution by a chlorine atom in the 7-position led to the highest activity.

EXPERIMENTAL.

Notes on the Preparation of the Substituted Anthranilic Acids and/or their Derivatives.—Methyl 5-chloroanthranilate (as III: R′ = Cl, R″ = H). Direct chlorination of methyl anthranilate (405 g.) by Freundler's method (*loc. cit.*) gave methyl 3:5-dichloroanthranilate (174 g.) and methyl 5-chloroanthranilate (200 g.). The latter had m. p. 67—69° after recrystallisation from light petroleum (b. p. 60—80°), and contained a trace of methyl anthranilate which did not interfere with the preparation of 6-chloro-4-hydroxyquinazoline.

4-Chloroanthranilic acid (III; R′ = H, R″ = Cl) *and 4-nitroanthranilic acid* (III; R′ = H, R″ = NO_2). See Curd *et al.*, forthcoming communication.

5-Methoxyanthranilic acid (III; R′ = OMe, R″ = H). 2-Nitro-5-methoxybenzaldehyde (Mason, *loc. cit.*) was oxidised by alkaline permanganate at 20° to the corresponding acid in 92% yield; m. p. 132—133°. The nitro-acid was reduced to 5-methoxyanthranilic acid with hot stannous chloride and hydrochloric acid, the tin removed by addition of ammonia, a slight excess of acetic acid added to the filtrate, and the amino-acid isolated by continuous extraction with ether in a percolator; yield, 90%; m. p. 144—147° (decomp.).

2-Nitro-4-methoxybenzamide (IX) *and 4-methoxyanthranilamide* (X). Concentrated sulphuric acid (1 l.) and water (1 l.) were mixed and heated to boiling. 2-Nitro-4-methoxyphenyl cyanide (200 g.) (Cook *et al.*, *loc. cit.*) was then added during 2 minutes, and the mixture hand-stirred and gently boiled for 4 minutes. It was then rapidly cooled, diluted to 8 l. with ice and water, set aside for 1 hour, and the crude *2-nitro-4-methoxybenzamide* (IX) collected and extracted with ammonia. The 2-nitro-4-methoxybenzoic acid (39 g.) in the extract was converted into the amide in the usual way (thionyl chloride, aqueous ammonia), and added to the main portion (m. p. 150—157°) which was then suspended in a solution of hydrated ferrous sulphate (2200 g.) in water (3 l.). The mixture was boiled and stirred, and a slight excess of ammonia gradually added. When cold, the solid was collected and extracted with boiling alcohol. The extract afforded *4-methoxyanthranilamide* (X) (137 g.), m. p. 150—153°. A portion of the nitro-amide (IX) had m. p. 161—161·5° after recrystallisation from water (charcoal), unchanged after recrystallisation from alcohol (Found: N, 14·6. $C_8H_8O_4N_2$ requires N, 14·3%). A portion of the anthranilamide (X) had m. p. 155—155·5° after recrystallisation from water (charcoal), unchanged after recrystallisation from alcohol (Found: N, 17·4. $C_8H_{10}O_2N_2$ requires N, 16·9%).

In one reduction the amide–iron oxide mixture was dried, pulverised, and extracted with boiling acetone in an automatic apparatus. Removal of the solvent gave *2-isopropylideneamino-4-methoxybenzamide*, m. p. 196—196·5° after recrystallisation from much water (charcoal) (Found: C, 63·8; H, 7·0; N, 14·0. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8; N, 13·6%). This anil was hydrolysed to the anthranilamide in 95% yield on boiling for 20 minutes with 25% sulphuric acid.

2-Nitro-4-methoxybenzoic acid. The cyanide (VIII) (20 g.) was refluxed for 2·5 hours with sulphuric acid (75 c.c.) and water (100 c.c.), the mixture cooled and diluted with water, and the 2-nitro-4-methoxybenzoic acid purified by dissolution in ammonia (yield, 20·4 g.); m. p. 195—197° after recrystallisation from water (charcoal).

4-Methoxyanthranilic acid (III; R′ = H, R″ = OMe). This acid was prepared from 2-nitro-4-

methoxybenzoic acid in the same way as its 5-methoxy-isomer above, and was precipitated from the ammoniacal solution on addition of acetic acid. Since the amino-acid is nearly completely decarboxylated by boiling for 0·5 hour with 2N-hydrochloric acid, the reduction was carried out as rapidly as possible at 85—90°, and the solution then immediately cooled; yield, 85%; m. p. 166—166·5° (decomp.) after recrystallisation from water (charcoal). The methyl ester was prepared by boiling the hydrochloride of the acid with 10% methanolic hydrogen chloride for 3 hours, and purified by washing with ammonia and recrystallisation from aqueous methanol (charcoal); m. p. 75—77°.

Preparation of the 4-Hydroxyquinazolines.—4-Hydroxyquinazoline (IV; R′ = R″ = H) was obtained in 55% yield by heating anthranilic acid (1 mol.) and formamide (2 mols.) at 135° for 3 hours and recrystallising the product from alcohol.

6-Chloro-4-hydroxyquinazoline (IV; R′ = Cl, R″ = H) was prepared by heating methyl 5-chloroanthranilate (188 g.) and formamide (200 c.c.) at 180° for 9 hours, the methanol produced being allowed to escape. The product was extracted with cold 3% aqueous sodium hydroxide, the insoluble material (31 g.) removed, and the hydroxyquinazoline (129 g.) obtained from the extract by addition of aqueous ammonium chloride followed by recrystallisation from acetic acid. The alkali-insoluble material gave on recrystallisation from alcohol a *compound*, m. p. 220—221·5°, which appeared to be a 6-chloro-4-hydroxydihydroquinazoline (Found: C, 52·6; H, 3·9; N, 15·0; Cl, 19·5. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·8; N, 15·3; Cl, 19·5%).

7-Chloro-4-hydroxyquinazoline (IV; R′ = H, R″ = Cl) was obtained in 56% yield by heating 4-chloroanthranilic acid (1 mol.) and formamide (2 mols.) at 160° for 3 hours and recrystallising the product from alcohol.

7-Nitro-4-hydroxyquinazoline (IV; R′ = H, R″ = NO_2) was prepared by heating 4-nitroanthranilic acid (150 g.) and formamide (180 c.c.) at 160° for 6 hours, extracting the product with hot 3% aqueous sodium hydroxide, and acidifying the solution with acetic acid; yield, 152 g.

4-Hydroxy-6-methoxyquinazoline (IV; R′ = OMe, R″ = H) was prepared by heating 5-methoxyanthranilic acid (84 g.) and formamide (100 c.c.) at 140° for 4·5 hours. The product was extracted with warm 10% aqueous sodium hydroxide, hydrochloric acid and then ammonia added, and the precipitated hydroxyquinazoline recrystallised from alcohol; yield, 75 g.

4-Hydroxy-7-methoxyquinazoline (IV; R′ = H, R″ = OMe). (*a*) 4-Methoxyanthranilamide (66 g.) and formic acid (*d*, 1·20; 70 c.c.) were refluxed at 140° for 2·5 hours. The product was treated with 5% aqueous sodium hydroxide, and hydrochloric acid followed by ammonia added to the extract; this precipitated the hydroxyquinazoline (66 g.).

(*b*) Methyl 4-methoxyanthranilate (4·2 g.) and formamide (4 c.c.) were heated at 140° for 3 hours. Extraction of the product with cold, dilute sodium hydroxide gave the hydroxyquinazoline (1·3 g.) and a compound (2·2 g.), m. p. 76—78°, which was probably the unchanged ester.

(*c*) 4-Methoxyanthranilic acid (5 g.) and formamide (3 c.c.) were heated at 140° for 3 hours. The product, boiled with alcohol and cooled, gave the hydroxyquinazoline (1 g.). The alcoholic filtrate was evaporated, and the residue extracted with ether in the presence of aqueous sodium hydroxide. The extract gave a solid (2·4 g.), m. p. 56·5—57·5° after recrystallisation from ether–light petroleum, which appeared to be formo-*m*-anisidide (Reverdin and Luc, *Ber.*, 1914, **47**, 1539, give m. p. 57°); it gave *m*-anisidine on hydrolysis with hydrochloric acid. The yield of hydroxyquinazoline was unaffected when the above reaction was carried out with a large excess of formamide. When the amino-acid (0·5 g.) and formamide (1 c.c.) were heated at 100° for 7 hours, the hydroxyquinazoline (0·03 g.) and an unidentified ammonia-soluble substance (0·15 g.), m. p. 189—190°, were obtained.

Preparation of the 4-Chloroquinazolines.—The hydroxyquinazoline (50—100 g., 1 mol.) was boiled with phosphorus pentachloride (1 mol.) and pure phosphorus oxychloride (150—300 c.c.) until the liquid was substantially clear (and no longer), the solvent removed by vacuum distillation, and the residue extracted with boiling light petroleum in a dry atmosphere. The extract deposited the 4-chloroquinazoline on cooling. This method gave products which were almost pure, and were collected as soon as the liquid was cold; otherwise, they tended to decompose. In this way, the following compounds were obtained, the reaction time, the b. p. of the light petroleum used for their isolation, and the yield being indicated in parenthesis: 4-chloroquinazoline (V; R′ = R″ = H) (2 hours, 60—80°, 45%); 4 : 6-dichloroquinazoline (V; R′ = Cl, R″ = H) (3 hours, 80—100°, 90%); *4 : 7-dichloroquinazoline* (V; R′ = H, R″ = Cl) (1 hour, 80—100°, 60%); *4-chloro-7-nitroquinazoline* (V; R′ = H, R″ = NO_2) (0·5 hour, 80—100°, 70%); *4-chloro-6-methoxyquinazoline* (V; R′ = OMe, R″ = H) (1·5 hours, 40—60°, 57%); *4-chloro-7-methoxyquinazoline* (V; R′ = H, R″ = OMe) (0·25 hour, 60—80°, 50%).

Preparation of the 4-Dialkylaminoalkylaminoquinazolines.—The appropriate 4-chloroquinazoline (10 g., 1 mol.) and the appropriate amine (1·1 mols.) were refluxed in alcohol (50 c.c.) for 0·5—1 hour; the required reaction had then occurred quantitatively. The material was then worked up in either of two ways: (*a*) the crystalline *4-dialkylaminoalkylaminoquinazoline monohydrochlorides*, which were occasionally deposited during the initial refluxing, were isolated either by direct addition of ether or by concentration and dissolution of the resulting syrup in acetone followed, if necessary, by addition of ether. Reference to these salts in Table II indicates when this method of working up was used for the particular compound in question. (*b*) The solutions were freed from solvent, the residues were taken up in acidulated water, sodium hydroxide was added, and the liberated *bases* were isolated by extraction with chloroform. When the bases were so hygroscopic as to be difficult to manipulate, or when it was desired to purify them through their salts, they were converted into their *disulphates* by dissolution in excess of concentrated alcoholic sulphuric acid followed by addition of acetone until just turbid; the salts crystallised out on being kept at 0° for a few hours.

The essential data concerning the above quinazolines and their derivatives are collected in Table II: the following notes give additional information concerning the properties and manipulation of certain of these compounds.

Simple quinazoline series. The dimethylaminopropylamino-compound was hygroscopic. The diethylaminoethoxypropylamino-compound was distilled (b. p. 196—200°/0·03 mm.) before the

TABLE II.

4-Substituted Quinazolines.

All compounds were colourless, except those of the nitro-series which were yellow (hydroxy-compound, brown).
All compounds are new except those indicated by a reference letter in the last column.

Benz-	Substituents: 4-Position.	Salt or hydrate.	S.	M. p.	Formula.	Analysis. Found, %. C.	H.	N.	Cl.	S.	Required, %. C.	H.	N.	Cl.	S.	Ref.
—	OH	—	A1	213°	$C_8H_6ON_2$	—	—	—	—	—	—	—	—	—	—	*a*
—	Cl	—	B1	98—100	$C_8H_5N_2Cl$	—	—	—	—	—	—	—	—	—	—	*b*
—	NH·[CH$_2$]$_2$·NEt$_2$	—	C1	124—125	$C_{14}H_{20}N_4$	68·7	8·5	22·9	—	—	68·9	8·2	23·0	—	—	—
—	NH·[CH$_2$]$_2$·NMe$_2$ [1]	—	B1	64—65	$C_{12}H_{16}N_4$	67·4	7·5	23·3	—	—	67·8	7·8	24·4	—	—	—
—	NH·[CH$_2$]$_2$·NHBu^a	—	—	Oil	$C_{14}H_{20}N_4$	70·1	8·4	21·3	—	—	69·8	8·5	21·7	—	—	—
—	NH·[CH$_2$]$_2$·NBu$^a_2$	—	B1	70—72	$C_{18}H_{28}N_4$	72·4	9·2	18·0	—	—	72·6	9·6	17·9	—	—	—
—	NH·CHMe·[CH$_2$]$_2$·NEt$_2$ [2]	—	B1	98	$C_{17}H_{26}N_4$	71·6	8·8	20·0	—	—	71·3	9·1	19·6	—	—	—
—	NH·[CH$_2$]$_2$·O·[CH$_2$]$_2$·NEt$_2$ [3]	—	B2	*ca.* 40	$C_{17}H_{26}ON_4$	67·2	8·5	18·1	—	—	67·5	8·6	18·6	—	—	—
—	NH·[CH$_2$]$_2$·N<[CH$_2$]$_4$>CH$_2$	H_2O	B1	106	$C_{16}H_{22}N_4,H_2O$	66·8	8·0	19·3	—	—	66·7	8·3	19·5	—	—	—
6-Cl	OH	—	D2	263—265	$C_8H_5ON_2Cl$	—	—	—	19·5	—	—	—	—	19·7	—	*c*
,,	Cl	—	B1	155—155·5	$C_8H_4N_2Cl_2$	—	—	—	35·4	—	—	—	—	35·7	—	*c*
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	B3	138—138·5	$C_{14}H_{19}N_4Cl$	—	—	20·2	—	—	—	—	20·1	—	—	—
,,	,,	HCl	A3	242—243	$C_{14}H_{19}N_4Cl,HCl$	53·5	6·4	—	11·6 [4]	—	53·3	6·4	—	11·3 [4]	—	—
,,	NH·[CH$_2$]$_2$·NMe$_2$	—	B3	123—124	$C_{13}H_{17}N_4Cl$	—	—	20·9	—	—	—	—	21·2	—	—	—
,,	,,	HCl	A2	203—204	$C_{13}H_{17}N_4Cl,HCl$	51·4	5·9	—	11·8 [4]	—	51·8	6·0	—	11·8 [4]	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	HCl	A2	162·5—163	$C_{16}H_{21}N_4Cl,HCl$	54·7	6·8	—	10·9 [4]	—	54·7	6·7	—	10·8 [4]	—	—
,,	NH·[CH$_2$]$_2$·NBu$^a_2$	—	B1	79—80	$C_{18}H_{29}N_4Cl$	—	—	16·1	—	—	—	—	16·1	—	—	—
,,	,,	HCl	A1	168·5—169·5	$C_{18}H_{29}N_4Cl,HCl$	59·5	7·8	—	9·1 [4]	—	59·2	7·8	—	9·2 [4]	—	—
,,	NH·CHMe·[CH$_2$]$_3$NEt$_2$	—	B1	112—113	$C_{17}H_{25}N_4Cl$	63·7	8·0	17·3	—	—	63·7	7·8	17·5	—	—	*c*
,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	B1	117—118	$C_{16}H_{21}N_4Cl$	—	—	18·4	—	—	—	—	18·4	—	—	—
,,	,,	HCl	A1	209—209·5 (decomp.)	$C_{16}H_{21}N_4Cl,HCl$	56·7	6·5	—	10·8 [4]	—	56·3	6·5	—	10·4 [4]	—	—
7-Cl	OH	—	A1	245 (decomp.)	$C_8H_5ON_2Cl$	53·1	3·1	15·8	—	—	53·2	2·8	15·5	—	—	—
,,	Cl	—	B4	132	$C_8H_4N_2Cl_2$	48·5	2·4	14·4	35·5	—	48·2	2·0	14·1	35·7	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	B1	125	$C_{14}H_{19}N_4Cl$	60·3	6·9	20·4	—	—	60·3	6·8	20·1	—	—	—
,,	NH·[CH$_2$]$_2$·NMe$_2$	—	B1	102	$C_{13}H_{17}N_4Cl$	59·4	6·2	21·6	—	—	59·0	6·4	21·2	—	—	—
,,	NH·[CH$_2$]$_3$·NEt$_2$	—	B1	105	$C_{15}H_{21}N_4Cl$	61·6	7·2	19·5	—	—	61·6	7·2	19·1	—	—	—
,,	NH·[CH$_2$]$_3$·NBu$^a_2$	—	B1	81—82	$C_{19}H_{29}N_4Cl$	65·1	8·4	16·0	—	—	65·4	8·3	16·1	—	—	—
,,	NH·CHMe·[CH$_2$]$_2$·NEt$_2$	—	B1	104—105	$C_{17}H_{25}N_4Cl$	63·8	7·7	17·8	—	—	63·7	7·8	17·5	—	—	—
,,	NH·[CH$_2$]$_2$·O·[CH$_2$]$_2$·NEt$_2$	—	B1	69—70	$C_{17}H_{25}ON_4Cl$	60·9	7·7	16·9	—	—	60·6	7·4	16·6	—	—	—
,,	NH·[CH$_2$]$_2$·N<[CH$_2$]$_4$>CH$_2$	0·5H_2O	B1	130—131	$C_{16}H_{21}N_4Cl,0·5H_2O$	61·3	7·3	18·1	—	—	61·3	7·0	17·9	—	—	—
7-NO_2	OH	—	D1	269—270	$C_8H_5O_3N_3$	—	—	—	—	—	—	—	—	—	—	*d*
,,	Cl	—	B4	146—147	$C_8H_4O_2N_3Cl$	—	—	—	16·6	—	—	—	—	16·9	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	E1	151—151·5	$C_{14}H_{19}O_2N_5$	—	—	23·9	—	—	—	—	24·2	—	—	—
,,	,,	HCl	A3	213—214 (decomp.)	$C_{14}H_{19}O_2N_5,HCl$	51·7	6·4	21·4	10·7 [4]	—	51·6	6·1	21·5	10·9 [4]	—	—
,,	NH·[CH$_2$]$_3$·NMe$_2$	—	E1	132—132·5	$C_{13}H_{17}O_2N_5$	—	—	25·5	—	—	—	—	25·5	—	—	—
,,	,,	HCl	A3	238—239	$C_{13}H_{17}O_2N_5,HCl$	50·3	5·7	—	11·6 [4]	—	50·1	5·8	—	11·4 [4]	—	—

3-X	„ NH·[CH$_2$]$_3$·NEt$_2$	—	B5	98—99	$C_{15}H_{21}O_2N_5$	—	—	23·1	—	—	—	—	23·1	—	—	—
	„ „	HCl	A2	194·5—195·5	$C_{15}H_{21}O_2N_5$,HCl	53·1	7·0	20·3	10·5 [4]	—	53·0	6·5	20·6	10·5 [4]	—	—
	„ NH·[CH$_2$]$_3$·NBu$^a_2$	—	B1	79—80	$C_{19}H_{29}O_2N_5$	—	—	19·2	—	—	—	—	19·5	—	—	—
	„ „	HCl	A2	180·5—182	$C_{19}H_{29}O_2N_5$,HCl	58·0	7·4	—	9·3 [4]	—	57·7	7·6	—	9·0 [4]	—	—
	„ NH·CHMe·[CH$_2$]$_3$·NEt$_2$	—	E2	107—109	$C_{17}H_{25}O_2N_5$	—	—	21·4	—	—	—	—	21·1	—	—	—
	„ „	HCl	A2	176—177	$C_{17}H_{25}O_2N_5$,HCl	55·8	7·2	—	10·0 [4]	—	55·5	7·1	—	9·7 [4]	—	—
	„ NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	—	—	69—71	$C_{17}H_{25}O_3N_5$	58·6	7·4	—	—	—	58·8	7·2	—	—	—	—
	„ „	H_2O	C1	70—71	$C_{17}H_{25}O_3N_5$,H_2O	56·2	7·4	19·5	—	—	55·9	7·4	19·2	—	—	—
	„ „	HCl	A2	142—143	$C_{17}H_{25}O_3N_5$,HCl	53·7	7·1	—	9·3 [4]	—	53·2	6·8	—	9·3 [4]	—	—
	„ NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	E1	139—140	$C_{16}H_{21}O_2N_5$	—	—	22·6	—	—	—	—	22·2	—	—	—
	„ „	HCl	A1	200—201	$C_{16}H_{21}O_2N_5$,HCl	54·4	6·6	—	10·3 [4]	—	54·6	6·3	—	10·1 [4]	—	—
	6-OMe OH	—	A1	242—243	$C_9H_8O_2N_2$	61·5	4·9	15·8	—	—	61·4	4·5	15·9	—	—	—
	„ Cl	—	B1	105—107	$C_9H_7ON_2Cl$	56·0	3·8	14·1	—	—	55·5	3·6	14·4	—	—	—
	„ NH·[CH$_2$]$_3$·NEt$_2$	—	B3	119—120	$C_{15}H_{23}ON_4$	—	—	20·6	—	—	—	—	20·4	—	—	—
	„ „	HCl	A2	213—214	$C_{15}H_{23}ON_4$,HCl	—	—	—	11·6 [4]	—	—	—	—	11·4 [4]	—	—
	„ „	$2H_2SO_4$	A3	162—164	$C_{15}H_{23}ON_4$,$2H_2SO_4$	38·6	5·4	11·8	—	12·7	38·3	5·5	11·9	—	13·6	—
	„ NH·[CH$_2$]$_3$·NMe$_2$	—	E2	132—133	$C_{14}H_{20}ON_4$	65·1	7·8	21·6	—	—	64·6	7·7	21·5	—	—	—
	„ NH·[CH$_2$]$_3$·NEt$_2$	—	B1	96—97	$C_{16}H_{24}ON_4$	—	—	19·6	—	—	—	—	19·4	—	—	—
	„ „	$2H_2SO_4$	A3	187—190	$C_{16}H_{24}ON_4$,$2H_2SO_4$	39·9	6·0	11·7	—	12·6	39·7	5·8	11·6	—	13·2	—
	„ NH·[CH$_2$]$_3$·NBu$^a_2$	—	B1	78·5—79·5	$C_{20}H_{32}ON_4$	69·6	9·5	—	—	—	69·8	9·3	—	—	—	—
	„ „	$2H_2SO_4$	A5	170—171	$C_{20}H_{32}ON_4$,$2H_2SO_4$	44·9	6·9	10·1	—	—	44·4	6·7	10·4	—	—	—
	„ NH·CHMe·[CH$_2$]$_3$·NEt$_2$	H_2O	E2	144—147	$C_{16}H_{26}ON_4$,H_2O	64·8	8·8	17·2	—	—	64·7	9·0	16·8	—	—	—
	„ NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	B3	110—111	$C_{17}H_{24}ON_4$	68·2	8·1	19·2	—	—	68·0	8·0	18·7	—	—	—
	„ „	$2H_2SO_4$	A4	214—217	$C_{17}H_{24}ON_4$,$2H_2SO_4$	40·6	5·6	11·1	—	—	41·1	5·7	11·3	—	—	—
	7-OMe OH	—	A1	257—258	$C_9H_8O_2N_2$	61·0	4·4	16·0	—	—	61·4	4·5	15·9	—	—	—
	„ Cl	—	B1	141—142	$C_9H_7ON_2Cl$	—	—	14·6	18·0	—	—	—	14·4	18·3	—	—
	„ NH·[CH$_2$]$_3$·NEt$_2$	—	B5	109—110	$C_{16}H_{24}ON_4$	65·4	8·1	20·7	—	—	65·7	8·0	20·4	—	—	—
	„ NH·[CH$_2$]$_3$·NMe$_2$	—	C2	126—127	$C_{14}H_{20}ON_4$	64·4	7·6	22·0	—	—	64·6	7·7	21·5	—	—	—
	„ NH·[CH$_2$]$_3$·NEt$_2$	—	C3	65—66	$C_{16}H_{24}ON_4$	66·4	8·4	19·6	—	—	66·7	8·3	19·4	—	—	—
	„ „	$2H_2SO_4$	A3	186—188	$C_{16}H_{24}ON_4$,$2H_2SO_4$	40·5	5·8	11·6	—	13·5	39·7	5·8	11·6	—	13·2	—
	„ NH·[CH$_2$]$_3$·NBu$^a_2$	—	—	54—57	$C_{20}H_{32}ON_4$	—	—	16·8	—	—	—	—	16·3	—	—	—
	„ „	$2H_2SO_4$	A1	160—162	$C_{20}H_{32}ON_4$,$2H_2SO_4$	44·0	7·1	10·4	—	12·1	44·4	6·7	10·4	—	11·9	—
	„ NH·CHMe·[CH$_2$]$_3$·NEt$_2$	—	—	92—93	$C_{16}H_{26}ON_4$	68·4	8·8	17·6	—	—	68·4	8·9	17·7	—	—	—
	„ NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	—	—	63—65	$C_{16}H_{26}O_2N_4$	64·7	8·4	—	—	—	65·1	8·4	—	—	—	—
	„ „	H_2O	C3	65—67	$C_{16}H_{26}O_2N_4$,H_2O	61·9	8·7	16·0	—	—	61·7	8·6	16·0	—	—	—
	„ NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	E2	121—122	$C_{17}H_{24}ON_4$	67·9	8·0	19·0	—	—	68·0	8·0	18·7	—	—	—

[1] *Dipicrate*, m. p. 215—217° (from alcohol) (Found: C, 43·8; H, 3·9; N, 20·2. $C_{13}H_{16}N_4$, $2C_6H_3O_7N_3$ requires C, 43·6; H, 3·5; N, 20·4%).

[2] *Dipicrate monohydrate*, m. p. 185—187° (from methanolic picric acid) (Found: C, 46·2; H, 4·3; N, 18·2. $C_{17}H_{26}N_4$,$2C_6H_3O_7N_3$,H_2O requires C, 46·3; H, 4·5; N, 18·4%).

[3] *Dimethiodide monohydrate*, m. p. 129—131° (from alcohol–acetone) (Found: C, 37·8; H, 5·4; N, 9·0; I, 42·4. $C_{19}H_{32}ON_4I_2$,H_2O requires C, 37·8; H, 5·6; N, 9·3; I, 42·1%).

[4] Ionic chlorine.

Solvents (S.) used for recrystallisation are indicated: A1, alcohol. A2, alcohol–acetone. A3, alcohol + trace of water. A4, alcohol + trace of water + H_2SO_4. A5, alcohol + H_2SO_4 followed by precipitation with ether. B1, light petroleum (b. p. 60—80°). B2, light petroleum (b. p. 60—80°) at − 10°. B3, light petroleum (b. p. 60—80°) + trace of chloroform. B4, light petroleum (b. p. 80—100°). B5, light petroleum (b. p. 60—80°) + trace of benzene. C1, dry ether. C2, ether–benzene. C3, ether–light petroleum (b. p. 60—80°) at − 18°. D1, acetic acid. D2, aqueous acetic acid. E1, benzene. E2, benzene–light petroleum (b. p. 60—80°).

a, Niementowski, *J. pr. Chem.*, 1895, **51**, 564. *b*, Gabriel and Stelzner, *Ber.*, 1896, **29**, 1314. *c*, Magidson and Golovchinskaya, *J. Gen. Chem. Russia*, 1938, **8**, 1797. *d*, Bogert and Klaber, *J. Amer. Chem. Soc.*, 1908, **30**, 808.

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recrystallisation indicated in Table II. The monobutylaminopropylamino-compound had b. p. 150—170°/0·0001 mm.

6-*Chloroquinazoline series.* During m. p. determinations on the diethylaminopropylamino-hydrochloride the melt occasionally solidified and then remelted at 186—187°. In the preparation of the dibutylaminopropylamino-hydrochloride, the cooled reaction mixture deposited waxy plates of a *compound* which had the same composition as γ-dibutylaminopropylamine dihydrochloride; m. p. 326—327° (decomp.) after recrystallisation from alcohol containing a trace of water (Found: C, 50·8; H, 11·1; N, 10·4; ionic Cl, 27·9. $C_{11}H_{26}N_2,2HCl$ requires C, 51·0; H, 10·8; N, 10·8; ionic Cl, 27·4%). Evidence that it was not identical with this diamine salt is: (*a*) a high m. p. and sparing solubility in pure alcohol would not be expected for such a salt; (*b*) addition of sodium hydroxide to its aqueous solution precipitated an almost odourless oil; (*c*) γ-dibutylaminopropylamine dihydrochloride was obtained, either by confinement over solid sodium hydroxide of a solution of the base in a slight excess of concentrated hydrochloric acid or by passing dry hydrogen chloride into a solution of the base in absolute ether, as an uncrystallisable syrup, an alcoholic solution of which failed to crystallise after being kept for several weeks, either alone or after being seeded with the unidentified compound. The latter was encountered during the preparation of all the dibutylaminopropylaminoquinazolines reported in this paper, and evidently arose from an impurity in the γ-dibutylaminopropylamine used.

7-*Nitroquinazoline series.* The diethylaminopropylamino-, diethylaminomethylbutylamino-, dibutylaminopropylamino-, and diethylaminoethoxypropylamino-bases became dark brown on exposure to light. The last compound was hygroscopic, and formed a syrup on exposure to air. The syrup, which was a monohydrate, ultimately crystallised, and the pure anhydrous base was prepared from the purified hydrate by desiccation over sulphuric acid.

6-*Methoxyquinazoline series.* On very humid days the diethylaminopropylamino- and dibutylaminopropylamino-bases were hygroscopic, rapidly forming syrups on exposure to air. The piperidinopropylamino-disulphate underwent marked dissociation to the monosulphate on recrystallisation from slightly aqueous alcohol; the dibutylaminopropylamino-disulphate also dissociated when recrystallised in the absence of free sulphuric acid, although much less readily than the previous salt. The diethylaminomethylbutylamino-base monohydrate withstood the drying action of sulphuric acid, and hence must have considerable stability.

7-*Methoxyquinazoline series.* The diethylaminopropylamino-, dibutylaminopropylamino-, and diethylaminoethoxypropylamino-bases were hygroscopic, and formed syrups on exposure to air. The syrup from the last compound crystallised as the monohydrate on standing, and the pure anhydrous base was obtained from the purified monohydrate by confinement in a vacuum over sulphuric acid. The dibutylaminopropylamino-base could not be satisfactorily recrystallised, and was therefore prepared from its purified disulphate by basification, extraction with pure ether, and removal of solvent, finally in a desiccator over sulphuric acid. The diethylaminomethylbutylamino-base was hygroscopic to an extent depending on the climatic conditions, and was purified through its oxalate as follows: the crude base, dissolved in acetone, was added to excess of a dilute solution of hydrated oxalic acid in acetone. Next day, the acetone was decanted, and the hard residue boiled with alcohol to give a crystalline solid, m. p. 166—167° (decomp.) unchanged after recrystallisation from alcohol containing a trace of water. The constitution of this *compound* was uncertain, but it appeared to be either the base mono-oxalate monoalcoholate monohydrate or the dihydrated monoethyl oxalate salt of the base (Found for material dried in a vacuum over sulphuric acid: C, 55·9; H, 7·9; N, 12·0. $C_{18}H_{28}ON_4,C_2H_2O_4,C_2H_6O,H_2O$ or $C_{16}H_{28}ON_4,C_4H_6O_4,2H_2O$ requires C, 56·2; H, 8·1; N, 11·9%). The base was recovered from this salt by dissolution in water, addition of sodium hydroxide, and extraction with pure ether.

2-*Chloro*-4-β-*diethylaminoethylaminoquinazoline* (XI; R = NH·$[CH_2]_2$·NEt_2).—A mixture of 2:4-dichloroquinazoline (6 g.), β-diethylaminoethylamine (4 g., 1·1 mols.), and alcohol (25 c.c.) was refluxed for 30 minutes. After cooling, the hydrochloride of the quinazoline (XI; R = NH·$[CH_2]_2$·NEt_2) which had separated was collected and crystallised from alcohol (yield, 90%), m. p. 202° in agreement with Curd, Landquist, and Rose (Part XIV, *loc. cit.*) (Found: N, 17·5. Calc. for $C_{14}H_{19}N_4Cl,HCl$: N, 17·8%).

2-*Amino*-4-β-*diethylaminoethylaminoquinazoline* (XII; R = NH·$[CH_2]_2$·NEt_2).—Several experiments in which the degree and period of heating were varied showed the following conditions to be the most satisfactory. The above hydrochloride (10 g.) was dissolved in a minimum amount of warm alcohol and then treated with cold alcohol previously saturated with ammonia (50 c.c.). The solution was filtered to remove precipitated ammonium chloride and then heated at 120° for 2 hours. Alcohol and ammonia were then removed from the product by evaporation at 20 mm. pressure, the residue was treated with 30% aqueous sodium hydroxide, and the base extracted with ether and dried (K_2CO_3). After removal of the ether, the residual solid was first extracted with hot light petroleum (b. p. 60—80°) to remove unchanged chloro-compound, and then recrystallised from acetone. The 2-*amino-quinazoline* was obtained as colourless crystals, m. p. 144° (Found: C, 65·3; H, 8·2; N, 26·8. $C_{14}H_{21}N_5$ requires C, 64·9; H, 8·1; N, 27·0%).

When this reaction was carried out at higher temperatures, *e.g.*, 170°, intractable gummy mixtures were produced, from which the only pure constituent isolated was 2:4-dihydroxyquinazoline.

2-*Chloro*-4-δ-*diethylamino*-α-*methylbutylaminoquinazoline* (XI; R = NH·CHMe·$[CH_2]_3$·NEt_2).—A mixture of 2:4-dichloroquinazoline (10 g.), δ-diethylamino-α-methylbutylamine (8 g., 1·1 mols.), and alcohol (50 c.c.) was refluxed for 1 hour, and the alcohol then evaporated. The residual syrup was treated with 30% aqueous sodium hydroxide, and the liberated base extracted with ether and dried. Evaporation of the ether gave an oily residue which solidified when vigorously stirred with chilled light petroleum (b. p. 40—60°); recrystallisation from light petroleum then furnished the 2-chloro-compound as colourless crystals, m. p. 98° (Found: C, 63·7; H, 8·0; N, 17·8. Calc. for $C_{17}H_{25}N_4Cl$: C, 63·7; H, 7·8; N, 17·5%) (yield, 37%).

2:4-*Dihydroxy*-7-*methoxyquinazoline and its Derivatives.*—Sodium cyanate (2·5 g.) was added rapidly to a suspension of pure 4-methoxyanthranilic acid (5 g.) in acetic acid (15 c.c.) at 60°. The mixture was heated on the steam-bath until effervescence ceased, diluted with water, and the 2-*carbamido*-4-*methoxy*-

benzoic acid collected, washed with boiling alcohol to remove any traces of unchanged amino-acid, and further purified by dissolution in ammonia and reprecipitation with acetic acid; m. p. 185—186° (decomp.) (Found: N, 13·1. $C_9H_{10}O_4N_2$ requires N, 13·3%). The carbamido-acid was then boiled for 1 minute with 20% sodium hydroxide (30 c.c.), cooled, and the sodium salt of the dihydroxyquinazoline collected. The salt was dissolved in boiling water, dilute sulphuric acid followed by ammonia added, and the precipitated 2 : 4-*dihydroxy-7-methoxyquinazoline* collected and washed with alcohol (yield, 4·3 g.); m. p. 299—301° (Found: N, 14·4. $C_9H_8O_3N_2$ requires N, 14·6%).

The dihydroxyquinazoline (10 g.), phosphorus pentachloride (22 g.), and pure phosphorus oxychloride (32 c.c.) were boiled until the liquid was clear (10 minutes), the solvent distilled off under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 60—80°) in a dry atmosphere. 2 : 4-*Dichloro-7-methoxyquinazoline* (7 g.) crystallised from the extract on cooling; m. p. 121—121·5° after recrystallisation from light petroleum (b. p. 60—80°) (Found: N, 12·2; Cl, 30·9. $C_9H_6ON_2Cl_2$ requires N, 12·2; Cl, 31·0%).

The dichloroquinazoline (5 g.) and β-diethylaminoethylamine (3·1 g., 1·2 mols.) were refluxed in alcohol (25 c.c.) for 10 minutes, the solvent was removed, the crystalline residue dissolved in water, aqueous sodium hydroxide added, and the liberated 2-*chloro*-4-β-*diethylaminoethylamino*-7-*methoxyquinazoline* isolated by extraction with chloroform and recrystallised from light petroleum (b. p. 60—80°) (yield, 5·8 g.); m. p. 108—109° (Found: N, 17·9; Cl, 11·4. $C_{15}H_{21}ON_4Cl$ requires N, 18·2; Cl, 11·5%).

The above chloroalkylamino-compound (1 g.) and alcohol saturated with ammonia at 0° (9 c.c.) were heated in a sealed tube at 160° for 3 hours. The solution was then distilled to remove solvent and ammonia, and the resulting syrup dissolved in dilute hydrochloric acid, basified with sodium hydroxide, and extracted with ether. Removal of the solvent left a small amount of resinous material which could not be crystallised, and from which crystalline salts could not be obtained.

This investigation was carried out as part of a wartime programme of antimalarial research sponsored by the Medical Research Council in collaboration with Imperial Chemical Industries Ltd. We are indebted to the former for grants (N. B. C. and G. M. G.) and to the latter for materials and for carrying out the biological tests. We are also greatly indebted to the workers of Imperial Chemical Industries for many discussions on the above work.

After this paper had been prepared for publication the following papers on quinazoline derivatives of related types appeared: Endicott, Wick, Mercury, and Sherrill (*J. Amer. Chem. Soc.*, 1946, **68**, 1299); Smith, Elisberg, and Sherrill (*ibid.*, p. 1301); Endicott, Alden, and Sherrill (*ibid.*, p. 1303); Price, Leonard, and Curtin (*ibid.*, p. 1305); Christensen, Graham, and Tomisek (*ibid.*, p. 1306), and Bunnett (*ibid.*, p. 1327).

University Chemical Laboratory, Cambridge. [*Received, September 10th*, 1946.]

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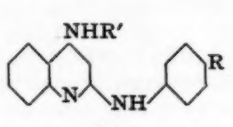
167. *Synthetic Antimalarials. Part XVII. Some Arylamino-aminoalkylaminoquinoline Derivatives.*

By F. H. S. Curd, C. G. Raison, and F. L. Rose.

The differential reactivities of the substituent groups in 2 : 4-dihydroxy- and 2 : 4-dichloroquinoline have been investigated and have been utilised for the preparation of a series of 2-arylamino-4-aminoalkylaminoquinolines (I) and their isomers (II). The former show the higher degree of antimalarial activity against *P. gallinaceum* in chicks, and this is discussed in the light of recent hypotheses.

The purpose of this communication is to report work leading to the synthesis of quinoline derivatives of types (I and II; R′ = aminoalkyl) that have not hitherto been investigated in the search for antimalarials based on the quinoline nucleus. The new compounds have an



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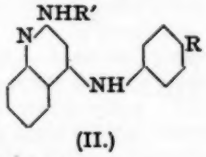

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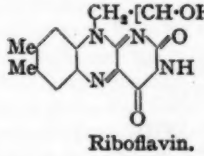
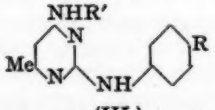


Riboflavin.



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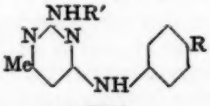

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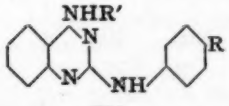

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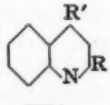
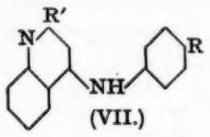


(VI.)

arylamino- and an aminoalkylamino-group attached to a heterocyclic ring system and in this respect are related to the pyrimidines of types (III) and (IV) described in Parts I, II, VI, and IX (*J.*, 1946, 343, 351, 370, 720) and the 2-arylamino-4-aminoalkylaminoquinazolines (V) (Part XIV, this vol., p. 775), all of which are actively plasmodicidal.

To achieve the synthesis of compounds of types (I) and (II) the possibility of a stepwise replacement of the groups R and R′ in a quinoline derivative of type (VI; R = R′ = OH or halogen) was first considered because the simplest of such compounds, namely 2 : 4-dihydroxyquinoline, was available as a dye intermediate. Further, literature methods were available for the preparation of a considerable number of nuclear substituted derivatives. Very little information was available, however, on the feasibility of carrying out the desired stepwise replacements. The reaction of 2 : 4-dihydroxyquinoline with a number of primary and secondary aliphatic amines at temperatures of 150—250° to give exclusively 4-amino- or 4-alkylamino-quinolines in high yields has been described (G.P. 681980). A similar reaction has now been found to occur with dialkylaminoalkylamines such as γ-diethylaminopropylamine giving 4-*γ-diethylaminopropylamino*-2-*hydroxyquinoline* (VI; R = OH, R′ = NH·$[CH_2]_3$·NEt_2). This compound reacted slowly with boiling phosphoryl chloride to give 2-*chloro*-4-*γ-diethylamino-propylaminoquinoline* (VI; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2) which was then condensed with *p*-chloroaniline by heating the reactants at *ca.* 200° for several hours, the product being 2-p-*chloroanilino*-4-*γ-diethylaminopropylaminoquinoline* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2). The condensation was also possible using an equimolecular proportion of *p*-chloroaniline in aqueous suspension in presence of hydrochloric acid (1·1 mols.), but a reaction time of 48 hours was needed to achieve a good yield. The orientation of these derivatives was demonstrated by the smooth reduction of the intermediate 2-chloro-4-γ-diethylaminopropylaminoquinoline with hydrogen and Raney nickel (cf. Whitmore and Revukas, *J. Amer. Chem. Soc.*, 1940, **62**, 1691; Krahler and Burger, *ibid.*, 1941, **63**, 2367) to give 4-*γ-diethylaminopropylaminoquinoline*, identical with a specimen prepared by the condensation of γ-diethylaminopropylamine with 4-chloroquinoline.

G.P. 681980 makes no mention of the condensation of 2 : 4-dihydroxyquinoline with arylamines, and we have found that the former is recovered completely unchanged after being heated with excess of aniline at 180—200° for 48 hours. In the presence of aniline hydrochloride, however, a smooth reaction occurred with the elimination of water and the formation (in 90% yield) of 4-anilino-2-hydroxyquinoline (VII; R = H, R′ = OH). Even so weak an acid as boric acid catalysed the condensation but less efficiently than hydrochloric acid. This compound has been described previously by v. Niementowski (*Ber.*, 1907, **40**, 4285) and by Dziewonski and Dymek (*Chem. Zentr.*, 1937, I, 1153). The former obtained it as one product of the reaction of benzoylacetic ester with anthranilic acid, noted its insolubility in alkali, and obtained 4-anilinoquinoline in poor yield from it on distillation with zinc dust. The latter authors heated 2 : 4-dianilinoquinoline with potassium hydroxide, obtained 4-anilino-2-hydroxyquinoline, and in addition the isomeric 2-anilino-4-hydroxyquinoline which is alkali soluble. They apparently used v. Niementowski's work as a basis for the orientation of the two isomers. We have found that 4-anilino-2-hydroxyquinoline reacts readily with phosphoryl chloride to yield 2-chloro-4-anilinoquinoline, and this compound, on reduction with hydrogen and Raney nickel, gave 4-anilinoquinoline, m. p. 196—198°, identical with an authentic specimen prepared from 4-chloroquinoline (cf. Ephraim, *Ber.*, 1893, **26**, 2229; Backeberg, *J.*, 1933, 618). The corresponding *p*-chloroanilino-compound (VII; R = R′ = Cl) was similarly obtained by first bringing 2 : 4-dihydroxyquinoline into reaction with *p*-chloroaniline in presence of its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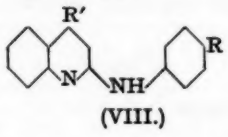
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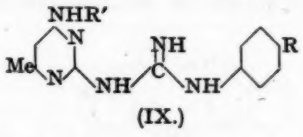
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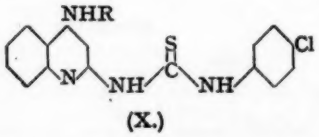
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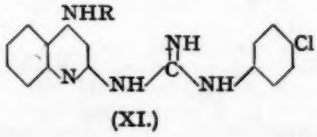
(XI.)

hydrochloride to give 4-p-*chloroanilino*-2-*hydroxyquinoline* (VII; R = Cl, R′ = OH) and then treating this with phosphoryl chloride. The 2-*chloro*-4-p-*chloroanilinoquinoline* thus obtained reacted readily with β-diethylaminoethylamine at 130—140° to give 4-*p*-chloroanilino-2-β-diethylaminoethylaminoquinoline and with γ-di-*n*-butylaminopropylamine to give 4-*p*-chloroanilino-2-γ-di-*n*-butylaminopropylaminoquinoline which were most readily isolated as their *dihydriodides*.

The reactions described above sufficed for the preparation of the two isomeric types of quinoline derivatives (I) and (II) of undoubted orientation, but before they were fully worked out a number of compounds of type (I) had been prepared starting from 2 : 4-dichloroquinoline. As far as we are aware the relative reactivities of the halogen atoms in this compound have been investigated previously only by Buchmann and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**, 1357) who heated it with potassium hydroxide in alcohol. Besides a small amount of 4-chlorocarbostyril they obtained approximately equal amounts of 4-chloro-2-ethoxy- and 2-chloro-4-ethoxy-quinoline. The reaction of (VI; R = R′ = Cl) with arylamines has now been investigated. When heated with an equimolecular amount of aniline, in alcohol or benzene in presence of anhydrous potassium carbonate, no reaction took place. This failure was understandable when it was found that the reaction of 2 : 4-dichloroquinoline and arylamines was catalysed by acid, so that in view of the formation of hydrochloric acid by the reaction the process was normally autocatalytic and indeed, in the absence of solvent, often violently exothermic. These general observations were later given confirmation by the work of Banks (*ibid.*, 1944, **66**, 1127). When equimolecular amounts of 2 : 4-dichloroquinoline and aniline, in acetic acid solution, were warmed together on the steam-bath, only a mildly exothermic reaction took place. The product was a mixture, but the only pure compound that could be isolated (in 53% yield) was 4-chloro-2-anilinoquinoline. This gave a considerable depression in melting point with 2-chloro-4-anilinoquinoline, whilst on reduction with hydrogen and Raney nickel it gave a substance, m. p. 102—103°, conforming to the description of 2-anilinoquinoline recorded in the literature (Friedländer and Weinberg, *Ber.*, 1885, **18**, 1532; Goldschmidt and Meissler, *ibid.*, 1890, **23**, 277). A number of other arylamines were then condensed with 2 : 4-dichloroquinoline to give products of type (VIII; R′ = Cl) which on heating with aminoalkylamines afforded compounds of type (I). Thus (VI; R = R′ = Cl) and *p*-chloroaniline led to 4-*chloro*-2-p-*chloroanilinoquinoline* which when condensed with γ-diethylaminopropylamine gave (I; R = Cl, R′ = $[CH_2]_3$·NEt_2) identical with that made from 2-chloro-4-γ-diethylaminopropylaminoquinoline and *p*-chloroaniline.

When tested against *P. gallinaceum* in chicks, 2-*p*-chloroanilino-4-β-diethylaminoethylamino- and 4-γ-diethylaminopropylamino-quinoline showed activity comparable with that of the analogous pyrimidines of type (III) but a certain lack of parallelism between the two series was observed when further variations in the arylamino- and aminoalkylamino-groups were investigated. An even greater divergence was noticeable between the quinoline derivatives of type (II) and the pyrimidine derivatives of type (IV), for the high activity of (IV; R = Cl, R′ = $[CH_2]_3$·NBu^n_2) (Part VI, *loc. cit.*) contrasted most markedly with the very low order of activity shown by (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2). This led us to examine the possibility that the activity of compounds of type (I) might be unconnected with their relationship to type (III), and this appeared to be a likely possibility since quinolines of types (I) and (II) do not allow conjugation between the pendant aryl and aminoalkyl groups *via* alternate carbon and nitrogen atoms as a result of either prototropy or resonance which, from our earlier work, we had come to believe might be a significant factor in the activity of our pyrimidine and diguanide types (Part XII, this vol., p. 154).

Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) has reported that 4-δ-diethylamino-α-methylbutylamino-6-methoxyquinoline possesses antimalarial properties, and other work carried out in these laboratories (to be published) had shown that 4-dialkylaminoalkylaminoquinolines in general possessed such properties. It therefore seemed conceivable that the activity of quinolines of type (I) might be due to their being 4-dialkylaminoalkylaminoquinolines carrying a grouping in the 2-position which made no direct contribution to the antimalarial activity and at the same time was not markedly deactivating. This possibility was further illustrated by the antimalarial results obtained with some of the intermediates, containing a dialkylaminoalkylamino-group in the 4-position, used in the synthetic work described in this paper. Thus whereas 4-γ-diethylaminopropylamino-2-hydroxy- and 2-chloro-4-γ-diethylaminopropylamino-quinoline were without activity at high doses, 2-*amino*-4-β-*diethylaminoethylaminoquinoline* and the corresponding γ-*diethylaminopropylamino*-derivative (VI; R = NH_2, R′ = NH·$[CH_2]_3$·NEt_2) (see later) showed considerable antimalarial activity. In this connection the work of Gilman and Spatz (*Iowa State College J. Sci.*, 1942, **17**, 129; *J. Amer. Chem. Soc.*, 1944, **66**, 621), knowledge of which only reached us when our own work was largely completed, is perhaps relevant. They have reported activity in certain 4-dialkylaminoalkylamino-2-arylquinolines prepared as " open chain models " of mepacrine, but do not provide any substantial proof that the activity of the compounds is in fact due to their relationship to mepacrine. They can equally well be regarded simply as modified 4-dialkylaminoalkylaminoquinolines.

This point was examined further in respect of our own compounds by observing the effect on antimalarial activity of introducing substituents into type (I) with and without the presence of the 2-arylamino-group. Compounds of the latter type are described in G.P. 683692 and E.P. 481874, and we were ourselves at the time collecting information on such compounds. For this purpose we prepared 2-p-*chloroanilino*-4-*γ*-*diethylaminopropylamino*-7 : 8-*benzo*-, 7-*chloro*-2-p-*chloroanilino*-4-*γ*-*diethylaminopropylamino*-, and 2-p-*chloroanilino*-4-*γ*-*diethylaminopropylamino*-3-*methyl*-*quinoline*. 2 : 4-*Dichloro*-7 : 8-*benzoquinoline* did not react with *p*-chloroaniline in acetic acid solution on the steam-bath, but from the product obtained by heating the two reactants together in 2-ethoxyethanol at 160°, 4-*chloro*-2-p-*chloroanilino*-7 : 8-*benzoquinoline*, was obtained, in rather poor yield, and condensed with *γ*-diethylaminopropylamine. Methyl 4-chloroanthranilate was condensed with ethyl malonate in the presence of sodium methoxide and the product hydrolysed and decarboxylated to give 7-chloro-2 : 4-dihydroxyquinoline which was successively condensed with *γ*-diethylaminopropylamine and treated with phosphoryl chloride to yield 2 : 7-*dichloro*-4-*γ*-*diethylaminopropylaminoquinoline*; this reacted with *p*-chloroaniline to give 7-*chloro*-2-p-*chloroanilino*-4-*γ*-*diethylaminopropylaminoquinoline*. In attempting to prepare compounds of type (I) containing an additional 3-methyl or 3-ethyl substituent, difficulties were encountered which were probably due to steric hindrance. Both 2 : 4-dihydroxy-3-methyl- and -3-ethyl-quinoline condensed with *γ*-diethylaminopropylamine to give the expected 4-*γ*-diethylaminopropylamino-2-hydroxy-derivatives which when treated with phosphoryl chloride gave respectively 2-*chloro*-4-*γ*-*diethylaminopropylamino*-3-*methyl*- and -3-*ethyl*-*quinoline*; but whereas the former on heating with *p*-chloroaniline gave a product from which the desired 2-p-*chloroanilino*-4-*γ*-*diethylaminopropylamino*-3-*methylquinoline* could be isolated, the latter gave an intractable mixture. Further, both 2 : 4-dichloro-3-methyl- and -3-*ethyl*-*quinoline* condensed with *p*-chloroaniline in acetic acid solution at 100° to give respectively 4-*chloro*-2-p-*chloroanilino*-3-*methyl*- and -3-*ethyl*-*quinoline*, but, although the former condensed slowly with *γ*-diethylaminopropylamine at 190—200°, the latter hardly reacted with this amine or with β-diethylaminoethylamine at this temperature and at higher temperatures (up to 250° in sealed tubes) gave intractable products.

The antimalarial activities obtained with these compounds (see Table I) did not support the view that they functioned simply as modified 4-dialkylaminoalkylaminoquinolines, and the possibility, mentioned earlier, that they might then be related biologically to the pyrimidines of type (III) was re-examined.

In a previous paper in this series (Curd and Rose, *J.*, 1946, 362) it was shown that the antimalarial activity of compounds of type (III) was retained and in certain instances enhanced if the arylamino- was replaced by an arylguanidino-group to give type (IX). A similar modification was accordingly made in the quinolines of type (I) utilising a synthetic method originally worked out as an alternative procedure for the synthesis of compounds of type (IX) and related compounds, which we shall report in detail later. A 2-chloro-4-dialkylaminoalkylaminoquinoline was treated with ammonia in hot phenol to give the corresponding 2-amino-4-dialkylaminoalkylaminoquinoline (VI; R = NH_2, R′ = dialkylaminoalkylamino) which was then condensed with *p*-chlorophenyl *iso*thiocyanate. The 2-*p*-chlorophenylthioureido-compound (X) thus obtained was desulphurised in the presence of alcoholic ammonia by means of mercuric oxide to give the 2-*p*-chlorophenylguanidino-derivative (XI). 2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*- and -4-*γ*-*diethylaminopropylamino*-*quinoline* were prepared in this way, but both failed to show antimalarial activity at tolerated doses. The corresponding thioureido-compounds of type (X) were likewise without demonstrable activity.

Attempts to prepare compounds of type (XI) by condensation of the appropriate 2-chloro-4-dialkylaminoalkylaminoquinoline with *p*-chlorophenylguanidine were unsuccessful. The chloroquinoline was recovered unchanged from trial condensations at temperatures at which ammonia was copiously evolved by breakdown of the guanidine.

Reviewing the results obtained with these compounds it is not possible to draw any very definite conclusion concerning the chemotherapeutic relationship of the quinolines of types (I) and (II) with the pyrimidines of types (III) and (IV) respectively. So far, we have considered this relationship only from the point of view of the chemical hypotheses followed in developing the discovery of antimalarial activity in the pyrimidine of types (III) and (IV). In earlier papers, however, we have discussed the possibility that antiplasmodial activity of these latter types may be associated with a growth antagonism arising from their formal structural similarity to the riboflavin molecule. Examination of the formulæ of (I) and (II) on this basis shows the former to bear the closer structural resemblance to the growth factor. This holds whether the pyrimidine ring of (I) is considered to correspond to the pyrimidine ring or to the benzene ring of

TABLE I.

Antimalarial activities.

The activities are the results of tests against *P. gallinaceum* in chicks and are expressed in the same way as in Part I (*J.*, 1946, 343). The full biological results will be published elsewhere.

Ref. No.	Substance.	Dose (mg./kg.).	Activity.
3627	4-*p*-Chloroanilino-2-β-diethylaminoethylaminoquinoline dihydriodide	400	+
3628	2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinoline dihydriodide	120	++
		80	+ to ++
		40	+
4006	2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinoline dihydrochloride	60	+
		40	±
		20	−
4011	2-*p*-Chloroanilino-4-γ-diethylaminopropylaminoquinoline dihydrochloride	60	+ to ++
		40	+
4321	2-*p*-Anisidino-4-β-diethylaminoethylaminoquinoline dihydriodide	120	+
		80	+
4322	2-*p*-Toluidino-4-β-diethylaminoethylaminoquinoline	100	++
		50	+
4323	2-β-Naphthylamino-4-β-diethylaminoethylaminoquinoline dihydriodide	160	+
		80	+
4324	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-7 : 8-benzoquinoline dihydrochloride	400	−
4342	2-*p*-Chloroanilino-4-γ-dimethylaminopropylaminoquinoline dihydrochloride	60	+ to ++
		40	+
4385	2-*p*-Chloroanilino-4-γ-piperidinopropylaminoquinoline dihydrochloride	60	+ to ++
	chloride	40	−
4612	2-*p*-Nitroanilino-4-γ-diethylaminopropylaminoquinoline dihydrochloride	80	+ to ++
		40	−
4623	7-Chloro-2-*p*-chloroanilino-4-γ-diethylaminopropylaminoquinoline	160	+
		80	+
		40	+
4627	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylaminoquinoline dihydriodide	400	+
		200	±
4665	2-*p*-Chloroanilino-4-δ-diethylaminobutylaminoquinoline dihydrochloride	80	+ to ++
		60	+
		40	+
4921	2-(6′-Bromo-β-naphthylamino)-2-γ-diethylaminopropylaminoquinoline	120	+
5092	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-3-methylquinoline	160	+
		80	−
5129	2-*p*-Chloroanilino-4-δ-diethylamino-α-methylbutylaminoquinoline	80	+
		40	+
5226	2-*p*-Chlorophenylthioureido-4-γ-diethylaminopropylaminoquinoline	160	−
		80	−
5276	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylaminoquinoline	80	−
		40	−
5463	2-*p*-Chlorophenylthioureido-4-β-diethylaminoethylaminoquinoline	160	−
		80	−
5477	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylaminoquinoline	160	−
		80	−
3738	4-γ-Diethylaminopropylamino-2-hydroxyquinoline	600	−
5099	2-Chloro-4-γ-diethylaminopropylaminoquinoline	160	−
5123	2-Amino-4-γ-diethylaminopropylaminoquinoline	80	++
		40	+
		20	−
5534	2-Amino-4-β-diethylaminoethylaminoquinoline	80	++
		40	++

riboflavin (in the latter case the fuzed benzene ring of the quinoline nucleus will correspond to the 6 : 7-dimethyl grouping in riboflavin, and examples of such a biological equivalence are provided among the polycyclic carcinogenic substances). This view affords some explanation of the variations in biological activity which occur on further substitution or modification of type (I). For instance, while type (IX) retains the property of being able to function as a riboflavin antagonist, the conversion of type (I) into type (XI) probably increases the total dimensions of the molecule to such an extent that a relationship with riboflavin is no longer discernible.

EXPERIMENTAL.

4-γ-Diethylaminopropylamino-2-hydroxyquinoline (VI; R = OH, R′ = NH·[CH_2]$_3$·NEt_2).—2 : 4-Dihydroxyquinoline (32·2 g., 1 mol.) and γ-diethylaminopropylamine (52 g., 2 mols.) were heated under reflux by means of an oil-bath at 170—180° for 18 hours. The cooled mixture was lixiviated

with water, and the product collected and washed with water. It was then extracted with dilute acetic acid and the filtered extract made alkaline with ammonia to reprecipitate the *compound* as an oil which rapidly solidified (yield, 68%). It formed colourless needles from aqueous alcohol, m. p. 174—175° (Found: C, 70·9; H, 8·6; N, 15·3. $C_{16}H_{23}ON_3$ requires C, 70·3; H, 8·4; N, 15·4%). It is insoluble in alkalis.

4-*β*-*Diethylaminoethylamino*-2-*hydroxyquinoline* (VI; R = OH, R′ = NH·[CH$_2$]$_2$·NEt$_2$).—2 : 4-Dihydroxyquinoline (80 g.) and *β*-diethylaminoethylamine (84 g., 1·45 mols.) were heated under reflux with stirring at 170—180° for 27 hours. After cooling, the mixture was extracted with dilute acetic acid and filtered from insoluble material (unchanged 2 : 4-dihydroxyquinoline, 32·6 g.). The acetic acid extract was made alkaline with ammonia which precipitated the product as an oil. This gradually solidified (yield, 56·8 g.), and subsequent purification by crystallisation from aqueous acetone gave 4-*β*-*diethylaminoethylamino*-2-*hydroxyquinoline*, m. p. 61—63° (Found: C, 61·1; H, 8·4; N, 13·8. $C_{15}H_{21}ON_3,2H_2O$ requires C, 61·0; H, 8·5; N, 14·2%).

2-*Chloro*-4-*γ*-*diethylaminopropylaminoquinoline* (VI; R = Cl, R′ = NH·[CH$_2$]$_3$·NEt$_2$).—4-*γ*-Diethylaminopropylamino-2-hydroxyquinoline (134 g.) and phosphoryl chloride (268 c.c.) were boiled under reflux for 20 hours and the solution cooled and poured on ice. The oil liberated on basification with 40% potassium hydroxide solution was extracted with ether and the ethereal extract filtered, dried (Na_2SO_4), and evaporated. The residual *chloro*-compound, purified by vacuum distillation, had b. p. 193—194°/0·2 mm., 180—182°/0·08 mm., and crystallised on standing (yield, 68%). It then separated from light petroleum (b. p. 40—80°) as colourless prisms, m. p. 51—52° (Found: C, 66·0; H, 7·4; N, 14·4; Cl, 12·1. $C_{16}H_{22}N_3Cl$ requires C, 65·9; H, 7·55; N, 14·4; Cl, 12·2%). The *dipicrate* crystallised from 2-ethoxyethanol in fine yellow needles, m. p. 193—194° (Found: N, 16·5; Cl, 4·8. $C_{16}H_{22}N_3Cl,2C_6H_3O_7N_3$ requires N, 16·8; Cl, 4·75%).

4-*γ*-*Diethylaminopropylaminoquinoline* (VI; R = H, R′ = NH·[CH$_2$]$_3$·NEt$_2$).—(*a*) 2-Chloro-4-*γ*-diethylaminopropylaminoquinoline in alcohol solution was shaken with hydrogen, Raney nickel, and potassium hydroxide (1 mol.), absorption of hydrogen ceasing when 1 mol. of hydrogen had been taken up. After filtration and evaporation to dryness the residue was treated with water and sodium hydroxide, and extracted with chloroform. Evaporation of the dried (K_2CO_3) extract left an oil, purified by vacuum distillation, b. p. 171—172°/0·15 mm. (yield, 65%) (Found: N, 15·8. $C_{16}H_{23}N_3$ requires N, 16·3%), which crystallised on adding water to form a *hydrate*, m. p. 57° not depressed by an authentic specimen prepared according to method (*b*) (Found: C, 69·5; H, 8·6. $C_{16}H_{23}N_3,H_2O$ requires C, 69·8; H, 9·1%).

(*b*) 4-Chloroquinoline (1·95 g.), *γ*-diethylaminopropylamine (3 c.c.), and potassium iodide (0·05 g.) were stirred and heated at 180° for 8 hours. The resulting mixture after being cooled was extracted with 10% acetic acid containing sodium acetate (0·5 g.), and the extract treated with decolorising carbon, filtered, and made alkaline with sodium hydroxide. The product, isolated with ether, had b. p. 173—174°/0·15 mm. and gave the hydrate, m. p. 56°. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as pale yellow needles, m. p. 180—182° (Found: C, 47·2; H, 4·1; N, 18·0. $C_{16}H_{23}N_3,2C_6H_3O_7N_3$ requires C, 47·0; H, 4·1; N, 17·6%).

2-*Chloro*-4-*β*-*diethylaminoethylaminoquinoline* (VI; R = Cl, R′ = NH·[CH$_2$]$_2$·NEt$_2$).—Prepared by careful addition of phosphoryl chloride to the dihydrate of the corresponding hydroxy-compound, followed by boiling for 18 hours and working up in the manner described for the corresponding *γ*-diethylaminopropylamino-derivative, this was obtained as a faintly yellow viscous oil, b. p. 183—184°/0·07 mm., which crystallised on addition of water to give the *hydrate* (yield, 36·6 g.) which crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 80—82° (Found: C, 60·9; H, 7·2; Cl, 11·6. $C_{15}H_{20}N_3Cl,H_2O$ requires C, 60·9; H, 7·45; Cl, 12·0%).

4-*Anilino*-2-*hydroxyquinoline* (VII; R = H, R′ = OH).—2 : 4-Dihydroxyquinoline (8·05 g.), aniline (23·3 g., 5 mols.), and aniline hydrochloride (6·5 g., 1 mol.) were stirred and heated at 180—190° for 12 hours. After removal of excess of aniline by steam distillation, the crystalline residue was collected and extracted with hot dilute sodium hydroxide and then washed, first with water, and then with hot methanol to remove a violet-coloured impurity. 4-Anilino-2-hydroxyquinoline remained as slightly bluish-grey prisms, m. p. 319—321° unchanged on crystallisation from 2-ethoxyethanol (v. Niementowski, *loc. cit.*, gives m. p. 318°; Dziewoński and Dymek, *loc. cit.*, give m. p. 316°) (Found: N, 12·1. Calc. for $C_{15}H_{12}ON_2$: N, 11·9%).

The same product was obtained in 87% yield by using boric acid in place of aniline hydrochloride and heating for 40 hours, but without an acid catalyst no product was formed.

4-p-*Chloroanilino*-2-*hydroxyquinoline* (VII; R = Cl, R′ = OH).—2 : 4-Dihydroxyquinoline (40·25 g.), *p*-chloroaniline (160 g.), and *p*-chloroaniline hydrochloride (41·0 g.) were heated with stirring for 4 hours at 180—190°. While still warm, the mixture was stirred with warm methanol (150 c.c.), and the residue filtered off and washed with methanol until free from blue colour, to leave a colourless crystalline product. This was ground with hot water and then with dilute sodium hydroxide, filtered, washed with water, and dried (yield, 89%). It formed colourless crystals from 2-ethoxyethanol, m. p. 296—298° (Found: N, 10·6; Cl, 13·8. $C_{15}H_{11}ON_2Cl$ requires N, 10·35; Cl, 13·1%).

2-*Chloro*-4-*anilinoquinoline* (VII; R = H, R′ = Cl).—4-Anilino-2-hydroxyquinoline (10·6 g.) and phosphoryl chloride (25 c.c.) were heated at 110—120° for 1½ hours and the solution was then evaporated under reduced pressure at 50—60°. The remaining greenish-yellow solid was ground under alcohol, and the mixture made alkaline with ammonia, diluted with water, filtered, washed, and dried. The chloro-compound (yield, 98%) had m. p. 162—164° unchanged after crystallisation from methanol from which it separated as thick colourless prisms (Found: N, 11·4; Cl, 13·9. Calc. for $C_{15}H_{11}N_2Cl$: N, 11·0; Cl, 13·9%). v. Niementowski (*loc. cit.*) gives m. p. 156°.

When the chloro-compound (1·28 g.) in alcohol (50 c.c.) was shaken with hydrogen in presence of Raney nickel and potassium hydroxide (0·3 g.), absorption of 1 mol. of hydrogen took place fairly rapidly. The mixture was then filtered and the solvent evaporated. Digestion of the solid residue with water gave a product which after crystallisation from methanol had m. p. 196—198° undepressed by an authentic specimen prepared from 4-chloroquinoline and aniline (Found: C, 81·5; H, 5·2; N, 12·8. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%).

2-*Chloro*-4-p-*chloroanilinoquinoline* (VII; R = R′ = Cl), prepared in theoretical yield from 4-*p*-chloroanilino-2-hydroxyquinoline (58 g.) and phosphoryl chloride (150 c.c.) followed by working up in the manner described above for (VII; R = H, R′ = Cl), had m. p. 174—175° unchanged by crystallisation from alcohol (Found: N, 9·4. $C_{15}H_{10}N_2Cl_2$ requires N, 9·7%).

4-p-*Chloroanilino*-2-*β*-*diethylaminoethylaminoquinoline* (II; R = Cl, R′ = $[CH_2]_2$·NEt_2).—2-Chloro-4-*p*-chloroanilinoquinoline (14·5 g.) and *β*-diethylaminoethylamine (9·0 g.) were heated at 130—140° for 14 hours. The mixture was dissolved in warm dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The extract was shaken with 5% acetic acid, the acetic acid extract made alkaline, and the product again extracted with chloroform. After drying (K_2CO_3), evaporation of the solvent left the base as an uncrystallisable oil which gave a gelatinous hydrochloride but a crystalline *dihydriodide* by evaporation of an alcoholic hydriodic acid solution of the base. This salt crystallised from alcohol in stout colourless prisms, softening from 240° and decomposing at 248° (Found: C, 39·8; H, 3·9. $C_{21}H_{25}N_4Cl,2HI$ requires C, 40·3; H, 4·3%) (3627).

4-p-*Chloroanilino*-2-*γ*-*di*-n-*butylaminopropylaminoquinoline* (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2).—2-Chloro-4-*p*-chloroanilinoquinoline (9·35 g.), *γ*-*di*-*n*-butylaminopropylamine (10 g.), and powdered potassium iodide (0·1 g.) were heated and stirred at 150—160° for 6 hours. The resulting mixture was treated with warm sodium hydroxide, cooled, and extracted with chloroform. The residue left after evaporation of the chloroform was extracted with 5% acetic acid (200 c.c.), decanted from a little undissolved oil, and extracted with ether. The aqueous layer was made alkaline and extracted with chloroform. After removal of the chloroform from the dried extract, excess of amine was removed by heating to 200°/0·1 mm. and the residual base converted into its *dihydriodide* which was induced to crystallise by trituration with dilute alcohol and then recrystallised from methanol–ethyl acetate; m. p. 200—202° (Found: C, 45·1; H, 5·7; 1 mg. ≡ 0·76 mg. AgX. $C_{26}H_{35}N_4Cl,2HI$ requires C, 45·0; H, 5·3; 1 mg. ≡ 0·88 mg. AgX).

4-*Chloro*-2-*arylaminoquinolines* (VIII; R′ = Cl).—A mixture of 2 : 4-dichloroquinoline (0·1 g.-mol.), the appropriate arylamine (0·1 g.-mol.), and acetic acid (40 c.c.) was stirred and heated on the steam-bath for times varying from ½ hour to 2 hours. In some experiments (procedure *a*) fused sodium acetate was then added to neutralise the liberated hydrochloric acid and the mixture poured into water. In others (procedure *b*) the mixture was diluted with water to precipitate the hydrochloride which was then collected and boiled with methanolic ammonia followed by dilution with water. In either case, the precipitated base was collected when solid, dried, and crystallised to constant m. p. Table II gives details of the compounds prepared.

TABLE II.

4-Chloro-2-arylaminoquinolines (VIII; R′ = Cl)

R.	Procedure.	Yield (%).	Formula.	M. p.	Solvent.	Analysis. Found (%). N.	Found (%). Cl.	Reqd. or calc. (%). N.	Reqd. or calc. (%). Cl.
H	*a*	53	$C_{15}H_{11}N_2Cl$	162—163° *	alcohol (rhombic prisms)	10·6	14·6	11·0	13·95
Cl	*b*	50	$C_{15}H_{10}N_2Cl_2$	135—136	methanol (needles)	9·7	24·5	9·7	24·5
MeO	*a*	43	$C_{16}H_{13}ON_2Cl$	140	alcohol (needles)	10·1	12·0	9·85	12·4
Me	*a*	40	$C_{16}H_{13}N_2Cl$	115·5—116·5	methanol (stout prisms)	10·8	13·5	10·4	13·2
NO_2	*b*	43	$C_{15}H_{10}O_2N_3Cl$	263—265	dioxan (prisms)	13·7	12·0	14·0	11·85
2-*β*-Naphthylamino-derivative	*b*	34	$C_{19}H_{13}N_2Cl$	108—110	aq. methanol (needles and prisms)	9·8	11·7	9·2	11·65
2-(6′-Bromo-*β*-naphthylamino)-derivative	*b*	50	$C_{19}H_{12}N_2ClBr$	152—154	*n*-propanol	7·8	1 mg. ≡ 0·853 mg. AgX	7·3	1 mg. ≡ 0·864 mg. AgX

* Dziewoński and Dymek, *Chem. Zentr.*, 1938, II, 1953, give m. p. 161°.

Reductive Dehalogenation of 4-*Chloro*-2-*anilinoquinoline*.—4-Chloro-2-anilinoquinoline (1·28 g.) and potassium hydroxide (0·3 g.) in alcohol (50 c.c.) were shaken with hydrogen and Raney nickel. Absorption of hydrogen was rapid and ceased after the theoretical uptake had occurred. The solution was filtered from catalyst and evaporated and water was added. The resulting oil soon solidified and was filtered off and dried. Crystallisation from dilute methanol and then from light petroleum (b. p. 60—80°) gave 2-anilinoquinoline as glistening colourless plates, m. p. 102—103° (Found: C, 81·4; H, 5·3; N, 13·0. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%).

2-p-*Chloroanilino*-4-*γ*-*diethylaminopropylaminoquinoline* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2).—(*a*) 2-Chloro-4-*γ*-diethylaminopropylaminoquinoline (8·1 g.), *p*-chloroaniline (10·65 g.), and powdered potassium iodide (0·1 g.) were heated at 200° for 6 hours with stirring. The mixture was dissolved in hot dilute hydrochloric acid and the filtered solution cooled and made alkaline with sodium hydroxide. The precipitated product was isolated with chloroform and partitioned between 5% acetic acid (100 c.c.) and ether. The aqueous layer was made alkaline with sodium hydroxide and the product again extracted

with chloroform. After drying (K_2CO_3), removal of the chloroform left an oil which rapidly solidified and then crystallised from benzene–light petroleum and finally from benzene giving the *base* as colourless fine needles, m. p. 154—156° (Found: C, 69·2; H, 7·0; N, 14·9; Cl, 9·3. $C_{22}H_{27}N_4Cl$ requires C, 69·0; H, 7·05; N, 14·6; Cl, 9·35%). It was converted into the *dihydrochloride* by dissolving in alcohol, adding hydrochloric acid until the solution was acid to Congo-red, evaporating to dryness under reduced pressure at 50—60°, and then evaporating with benzene–alcohol to remove the last traces of hydrochloric acid. The solid residue then crystallised from alcohol–ethyl acetate in colourless fine needles, which were hydrated and decomposed above 110° (Found: C, 54·0; H, 6·7; N, 11·4; Cl′, 15·0. $C_{22}H_{27}N_4Cl,2HCl,2H_2O$ requires C, 53·7; H, 6·7; N, 11·4; Cl′, 14·5%). This salt is readily soluble in water.

(*b*) 2-Chloro-4-γ-diethylaminopropylaminoquinoline (5·15 g.), *p*-chloroaniline (2·25 g.), water (20 c.c.), ethanol (5 c.c.), and 10N-hydrochloric acid (1·7 c.c.) were refluxed together for 48 hours. After cooling and addition of sodium acetate, a little unreacted *p*-chloroaniline was removed by ether extraction. Basification of the aqueous layer precipitated a solid which was filtered off, dried, and crystallised from benzene giving the same product as in (*a*), m. p. and mixed m. p. 155—156° (yield, 4·3 g.).

(*c*) 4-Chloro-2-*p*-chloroanilinoquinoline (20 g.), γ-diethylaminopropylamine (18·0 g.), and powdered potassium iodide (0·3 g.) were heated with stirring in an oil-bath at 180—190° for 16 hours. A solution of the mixture in warm dilute hydrochloric acid was made alkaline with sodium hydroxide and extracted with chloroform. The solvent was removed, the residue digested with warm 50% acetic acid (250 c.c.), and the filtered solution basified and extracted with chloroform. After drying (K_2CO_3) and removal of the chloroform an oil was obtained which quickly solidified and was then crystallised from benzene (yield, 17·6 g.); it had m. p. 153—155°, and was identical with the compound made by methods (*a*) and (*b*) (Found: C, 68·6; H, 7·1%).

Using method (*c*) a number of other 2-arylamino-4-dialkylaminoalkylaminoquinolines were prepared. Details are given in Table III.

2 : 4-*Dichloro*-7 : 8-*benzoquinoline*.—2 : 4-Dihydroxy-7 : 8-benzoquinoline (78 g.) (prepared from α-naphthylamine and ethyl malonate, cf. E.P. 332911 and Baumgarten and Kärgel, *Ber.*, 1927, **60**, 832) and phosphoryl chloride (200 c.c.) were heated at 90—100° for ½ hour during which time hydrogen chloride was copiously evolved. The temperature was then raised to 120—125° and maintained for 3½ hours. The resulting clear solution was cooled and added to crushed ice with stirring. The precipitated product was filtered off, washed free from acid, dried, and refluxed with acetone (1 l.). After filtration from insoluble matter, the acetone was distilled off and the residue crystallised from ethyl acetate (yield, 48·5 g.). 2 : 4-*Dichloro*-7 : 8-*benzoquinoline* formed long colourless needles from acetone, m. p. 134—135° (Found: C, 63·0; H, 3·5; Cl, 28·3. $C_{13}H_7NCl_2$ requires C, 62·9; H, 2·8; Cl, 28·6%).

4-*Chloro*-2-p-*chloroanilino*-7 : 8-*benzoquinoline*.—2 : 4-Dichloro-7 : 8-benzoquinoline (24·8 g.), *p*-chloroaniline (12·7 g.), *p*-chloroaniline hydrochloride (0·1 g.), and 2-ethoxyethanol (30 c.c.) were heated in an oil-bath at 160° for 3·5 hours. The mixture was then cooled and diluted with water, and the precipitated product filtered off and dissolved in boiling alcohol (350 c.c.) with the addition of sufficient ammonia to give an alkaline reaction. The resulting solution was treated with an equal volume of water. The product, when solid, was collected, dried, and crystallised first from benzene and then from butanol (yield, 40%) giving needles, m. p. 160—162° (Found: Cl, 20·4. $C_{19}H_{12}N_3Cl_2$ requires Cl, 20·4%).

2-p-*Chloroanilino*-4-γ-*diethylaminopropylamino*-7 : 8-*benzoquinoline*.—The preceding chloro-compound (17·6 g.), γ-diethylaminopropylamine (13·5 g.), and powdered potassium iodide (0·3 g.) were heated at 175—185° with stirring for 24 hours. Worked up in the usual way for this type of compound the base was obtained as a glass which could not be induced to crystallise. It was therefore dissolved in hot acetone (100 c.c.), and hydrochloric acid added until the solution showed acidity to Congo-red. On cooling, the *dihydrochloride* crystallised out as a hydrate and was recrystallised from acetone–water, m. p. 108—110° (Found: C, 55·3; H, 6·4; N, 10·0; Cl′, 13·6. $C_{26}H_{29}N_4Cl,2HCl,3H_2O$ requires C, 55·8; H, 6·3; N, 10·0; Cl′, 12·7%).

7-*Chloro*-2 : 4-*dihydroxyquinoline*.*—This was prepared by a modification of a method for 2 : 4-dihydroxyquinoline described by Koller (*Ber.*, 1927, **60**, 1108). Methyl 4-chloroanthranilate (100 g.) (Hunn, *J. Amer. Chem. Soc.*, 1923, **45**, 1028), ethyl malonate (86·2 g.), and sodium methoxide (29 g.) were mixed in a flask fitted with a condenser arranged for distillation. After the mixture had been stirred at 70° until homogeneous (*ca.* 1 hour), the temperature was raised slowly to 140—150° and then maintained for 6 hours. Alcohol distilled and the mixture thickened, eventually becoming quite solid. After cooling, the mixture was repeatedly extracted with cold dilute sodium hydroxide and the extracts were acidified to precipitate what was probably methyl 7-chloro-2 : 4-dihydroxyquinoline-3-carboxylate (89 g.). This ester (35 g.) was hydrolysed and decarboxylated by heating on the steam-bath overnight with sodium hydroxide (13 g. in 350 c.c. water); after being filtered from a little insoluble material the filtrate was acidified. The precipitate was collected, washed, and boiled with dilute sodium carbonate solution, and the solution cooled, filtered, and acidified. 7-Chloro-2 : 4-dihydroxyquinoline was precipitated as an almost colourless powder, m. p. 332—340° (decomp.) (Found: N, 6·7; Cl, 18·5. Calc. for $C_9H_6O_2NCl$: N, 7·2; Cl, 18·2%). This substance has been prepared very recently by another modification of Koller's method by Lutz *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1285).

7-*Chloro*-4-γ-*diethylaminopropylamino*-2-*hydroxyquinoline*.*—7-Chloro-2 : 4-dihydroxyquinoline (30 g.) and γ-diethylaminopropylamine (41·2 g.) were heated at 170—180° for 20 hours and then worked up as described for 4-γ-diethylaminopropylamino-2-hydroxyquinoline to give the *compound* as practically colourless needles, m. p. 228—229° (Found: C, 62·2; H, 6·9; N, 13·9; Cl, 12·0. $C_{16}H_{22}ON_3Cl$ requires C, 62·4; H, 7·1; N, 13·7; Cl, 11·55%).

2 : 7-*Dichloro*-4-γ-*diethylaminopropylaminoquinoline*.*—The above hydroxy-compound (12 g.) and phosphoryl chloride (24 c.c.) were heated by means of an oil-bath at 130—140° for 16 hours followed by working up in the usual way for this type of compound to give the product, m. p. 82—87°, characterised as

* Experiments by Mrs. J. M. Wilson.

TABLE III.

2-Arylamino-4-aminoalkylaminoquinolines.

Substituent at 2.	Substituent at 4.	Derivative.	M. p.	Solvent; crystalline form.	Formula.	Analysis. Found (%). C.	H.	N.	Cl′.	Required (%). C.	H.	N.	Cl′.
p-Chloroanilino	NH·[CH$_2$]$_3$·NEt$_2$	—	B.p. 258°/0·1 mm.	Very viscous oil	—	—	—	—	—	—	—	—	—
		Dihydrochloride	169—171° (decomp.)	Alcohol–ethyl acetate; needles	$C_{21}H_{25}N_4Cl,2HCl,H_2O$	55·3	6·3	—	15·6	54·9	6·3	—	15·45
		Dihydriodide	253—254 (decomp.)	Alcohol–ethyl acetate; prisms	$C_{21}H_{25}N_4Cl,2HI$	40·1	4·4	—	—	40·3	4·3	—	—
p-Chloroanilino	NH·[CH$_2$]$_4$·NEt$_2$	Dihydrochloride	201—203 (decomp.)	Alcohol–ethyl acetate; needles	$C_{23}H_{29}N_4Cl,2HCl,H_2O$	56·8	6·4	11·8	14·9	56·6	6·8	11·5	14·6
p-Chloroanilino	NH·CHMe·[CH$_2$]$_3$·NEt$_2$ [1]	Dipicrate	230—232 (decomp.)	2-Ethoxyethanol-pyridine; yellow needles	$C_{24}H_{31}N_4Cl,2C_6H_3O_7N_3$	49·1	4·5	16·6	—	49·7	4·3	16·1	—
p-Chloroanilino *	NH·[CH$_2$]$_3$·NMe$_2$	Dihydrochloride	86—88 (decomp.)	Alcohol–ethyl acetate	$C_{20}H_{23}N_4Cl,2HCl,1·5H_2O$	52·9	6·3	12·2	15·0	52·8	6·2	12·3	15·6
p-Chloroanilino *	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	Dihydrochloride	86—88	Dilute hydrochloric acid	$C_{23}H_{27}N_4Cl,2HCl,5H_2O$	49·6	6·8	10·6	13·1	49·5	7·0	10·05	12·8
p-Anisidino	NH·[CH$_2$]$_3$·NEt$_2$	Dihydriodide	146—148 (decomp.)	Aqueous alcohol; needles	$C_{22}H_{28}ON_4,2HI,H_2O$	41·7	5·1	—	—	41·4	5·0	—	—
p-Toluidino	NH·[CH$_2$]$_3$·NEt$_2$	—	109—111	*cyclo*Hexane; prisms	$C_{22}H_{28}N_4,0·5H_2O$	74·4	7·8	16·0	—	74·0	8·1	15·7	—
p-Nitroanilino	NH·[CH$_2$]$_3$·NEt$_2$	Dihydrochloride	182—184 (softening at 172)	Alcohol–ethyl acetate	$C_{22}H_{27}O_2N_5,2HCl,4H_2O$	49·2	6·0	13·7	—	49·1	6·8	13·0	—
β-Naphthylamino	NH·[CH$_2$]$_3$·NEt$_2$	Dihydriodide	127—128	Methanol	$C_{25}H_{28}N_4,2HI,H_2O$	45·6	5·0	—	—	45·6	5·0	—	—
6-Bromo-β-naphthylamino	NH·[CH$_2$]$_3$·NEt$_2$	—	149—150	Benzene–light petroleum	$C_{26}H_{29}N_4Br$	65·9	5·8	11·8	—	65·4	6·1	11·7	—

[1] For biological test the picrate was dissolved in pyridine, the solution added to aqueous sodium hydroxide, and the base extracted with ether which was then thoroughly washed with sodium hydroxide and water, dried, and evaporated, giving the base as an oil. This was made soluble with lactic acid.

its *dipicrate* which crystallised from aqueous 2-ethoxyethanol and had m. p. 194—195° (Found: N, 15·8; Cl, 9·5. $C_{16}H_{21}N_3Cl_2,2C_6H_3O_7N_3$ requires N, 16·1; Cl, 9·1%).

*7-Chloro-2-p-chloroanilino-4-γ-diethylaminopropylaminoquinoline.**—2 : 7-Dichloro-4-γ-diethylaminopropylaminoquinoline (8·96 g.), *p*-chloroaniline (10·6 g.), and potassium iodide (0·1 g.) were heated for 8 hours at 200°. The mixture was treated with hot dilute hydrochloric acid, made alkaline with sodium hydroxide, and steam distilled to remove unchanged *p*-chloroaniline. The residual oil was separated and dissolved in 5% acetic acid, and the solution extracted with ether. Basification followed by isolation with chloroform then gave the *product* which crystallised from benzene–light petroleum as colourless laminæ, m. p. 144—145° (Found: C, 63·0; H, 6·1; N, 13·7; Cl, 17·1. $C_{22}H_{26}N_4Cl_2$ requires C, 63·3; H, 6·2; N, 13·4; Cl, 17·1%).

2 : 4-Dihydroxy-3-methylquinoline.—Aniline (46·5 g.) and ethyl methylmalonate (87 g.), contained in a flask fitted with a long condenser allowing only the liberated alcohol to escape, were heated at 230—240° for ½ hour, then at 290—300° for 1½ hours, and finally raised to 340° during ½ hour. The cooled mass was boiled with acetone (100 c.c.) for 10 hours and the insoluble material filtered off after cooling. It was then boiled with sodium carbonate solution (700 c.c. of 10%) for 10 minutes and cooled, and the solution was filtered and the product precipitated with hydrochloric acid (yield, 53%). Crystallised from 2-ethoxyethanol and then from butanol it formed almost colourless prisms, m. p. 265—268° (decomp.) (Found: C, 68·3; H, 4·9; N, 8·4. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·1; N, 8·0%) (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, give m. p. >270°).

2 : 4-Dichloro-3-methylquinoline.—2 : 4-Dihydroxy-3-methylquinoline (25 g.) and phosphoryl chloride (75 c.c.) were heated at 100—110° for ½ hour and then at 120—125° for 5 hours. The mixture was then cooled and poured on ice. The precipitated product was filtered off, washed free from acid with water, dried (yield, 29·7 g.), and crystallised from 80% alcohol, m. p. 90—91° (Found: Cl, 33·1. Calc. for $C_{10}H_7NCl_2$: Cl, 33·5%) (Gabriel and Gerhard, *loc. cit.*, give m. p. 83—84°).

4-γ-Diethylaminopropylamino-2-hydroxy-3-methylquinoline.—2 : 4-Dihydroxy-3-methylquinoline (20 g.) and γ-diethylaminopropylamine (30 g.) were heated at 180—190° for 22·5 hours and the mixture was cooled and poured into water. The *prodnct*, precipitated as an oil, soon solidified. It was collected, dissolved in 5% acetic acid, precipitated with ammonia, and dried at 60° (yield, 47·5%). It crystallised from aqueous alcohol as pale yellow stout prisms, m. p. 105—106° (Found: N, 14·7. $C_{17}H_{25}ON_3$ requires N, 14·6%).

4-γ-Diethylaminopropylamino-2-hydroxy-3-ethylquinoline, prepared in exactly the same manner from 2 : 4-dihydroxy-3-ethylquinoline (Baumgarten and Kärgel, *loc. cit.*) and γ-diethylaminopropylamine, crystallised from aqueous alcohol; m. p. 100—101° (Found: N, 14·2. $C_{18}H_{27}ON_3$ requires N, 14·0%).

2-Chloro-4-γ-diethylaminopropylamino-3-methylquinoline.—4-γ-Diethylaminopropylamino-2-hydroxy-3-methylquinoline (13·35 g.) and phosphoryl chloride (30 c.c.) were heated at 115—125° for 18 hours. Most of the excess of phosphoryl chloride was then removed under diminished pressure and the residue dissolved in water, made alkaline with potassium hydroxide, and extracted with ether. The dried ethereal extract was evaporated and the residual oil extracted with cold light petroleum (b. p. 40—60°) (100 c.c.), filtered, and evaporated. 2-Chloro-4-γ-diethylaminopropylamino-3-methylquinoline remained as an oil which could not be crystallised. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as fine yellow needles of indefinite melting point (*ca.* 160°) (Found: N, 16·6; Cl, 4·7. $C_{17}H_{24}N_3Cl,2C_6H_3O_7N_3$ requires N, 16·5; Cl, 4·65%).

4-Chloro-2-p-chloroanilino-3-methylquinoline.—2 : 4-Dichloro-3-methylquinoline (21·2 g.) and *p*-chloroaniline (12·75 g.) in acetic acid (40 c.c.) were heated on the steam-bath for 2 hours with stirring. Crystalline material was deposited during the reaction. This was collected after dilution with water, washed, and stirred overnight with methanol containing excess of ammonia. Water was then added, and the product collected, washed, and dried. This crude material was ground and extracted with cold dioxan leaving undissolved *2 : 4-di-p-chloroanilino-3-methylquinoline* (3·1 g.), m. p. 266—268° (Found: Cl, 18·0. $C_{22}H_{17}N_3Cl_2$ requires Cl, 18·0%). The dioxan filtrate from this di-condensation product was diluted with water and the precipitated material, initially an oil which gradually solidified, filtered off and crystallised from alcohol, giving *4-chloro-2-p-chloroanilino-3-methylquinoline* as colourless fine needles, m. p. 120—121° (Found: N, 9·3; Cl, 22·9. $C_{16}H_{12}N_2Cl_2$ requires N, 9·25; Cl, 23·4%) (yield, 15·85 g.).

2-p-Chloroanilino-4-γ-diethylaminopropylamino-3-methylquinoline.—(*a*) Crude 2-chloro-4-γ-diethylaminopropylamino-3-methylquinoline (9·65 g.), *p*-chloroaniline (12·1 g.), and potassium iodide (0·1 g.) were heated at 200° for 12 hours. The mass was dissolved in alcohol, and the solution made alkaline with sodium hydroxide and steam distilled. The residual oil was isolated with chloroform and shaken with 5% acetic acid (150 c.c.) and ether. The aqueous layer was separated and re-extracted with ether, and then made alkaline with sodium hydroxide and extracted with chloroform. Evaporation of the dried (K_2CO_3) extract left the base as an oil which could not be induced to crystallise. The picrate and hydrochloride likewise failed to crystallise. A solution of the base in dilute hydrochloric acid on treatment with perchloric acid gave the *perchlorate* which crystallised from alcohol in rosettes of colourless needles, m. p. 216—218° (Found: C, 46·1; H, 4·9; N, 9·7. $C_{22}H_{29}N_4Cl,2HClO_4$ requires C, 46·2; H, 5·2; N, 9·4%).

(*b*) 4-Chloro-2-*p*-chloroanilino-3-methylquinoline (10 g.), γ-diethylaminopropylamine (8·6 g.), and potassium iodide (0·15 g.) were heated under reflux in an oil-bath at 190—200° for 22 hours. When cool, the semi-solid mass was treated with aqueous sodium hydroxide and extracted with chloroform. After evaporation of the solvent the residue was stirred with 5% acetic acid (150 c.c.), filtered and extracted with ether. The acetic solution was then basified and extracted with chloroform. Evaporation of the dried chloroform extract left an oily base contaminated with γ-diethylaminopropylamine. This was removed by heating overnight at 120—130°/15 mm. and the residue dissolved in dilute hydrochloric acid and treated with perchloric acid to give the same perchlorate as in (*a*), m. p. and mixed m. p. 215—217° (Found: C, 45·7; H, 5·2%).

For biological testing the perchlorates from (*a*) and (*b*) were combined and treated with aqueous sodium hydroxide, and the liberated base was isolated with chloroform.

2-Chloro-4-γ-diethylaminopropylamino-3-ethylquinoline.—4-γ-Diethylaminopropylamino-2-hydroxy-3-ethylquinoline (15 g.) and phosphoryl chloride (35 c.c.) were heated at 115—125° for 16 hours followed by working up as described for the corresponding 3-methyl compound to give the product as an oil which could not be crystallised. It gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol as yellow plates, m. p. 144—146° (Found: N, 16·3; Cl, 4·6. $C_{16}H_{26}N_3Cl,2C_6H_3O_7N_3$ requires N, 16·2; Cl, 4·6%).

2 : 4-*Dichloro-3-ethylquinoline.*—2 : 4-Dihydroxy-3-ethylquinoline (50 g.) and phosphoryl chloride (150 c.c.) were heated with stirring at 100—110° for ½ hour and then at 120—125° for 4 hours. The cooled mixture was poured on ice and after being stirred for several hours the product was extracted with ether. Evaporation of the washed and dried ethereal extract gave an oil which was purified by vacuum distillation, b. p. 182—184°/21 mm. (yield, 88%) (Found: Cl, 31·0. $C_{11}H_9NCl_2$ requires Cl, 31·4%).

4-Chloro-2-p-chloroanilino-3-ethylquinoline.—2 : 4-Dichloro-3-ethylquinoline (22·6 g.), *p*-chloroaniline (12·75 g.), and acetic acid (40 c.c.) were heated on the steam-bath for 2 hours with stirring and then refluxed for 10 minutes. When cold, the mixture was diluted with water and made strongly acid to Congo-red with hydrochloric acid. The practically colourless crystalline powder thereby obtained was filtered off, washed with water, and heated on the steam-bath for 10 minutes with methanol (100 c.c.) and sufficient ammonia to give an alkaline reaction. Dilution with water gave a product which was filtered off, dried, and crystallised from alcohol; it was obviously a mixture (18·4 g.). Crystallisation from dioxan (40 c.c.) gave fine needles of 2 : 4-*di*-p-*chloroanilino-3-ethylquinoline* (3·6 g.), m. p. 224—226° (Found: Cl, 17·3. $C_{23}H_{19}N_3Cl_2$ requires Cl, 17·4%), and dilution with water the required *4-chloro-2-p-chloroanilino-3-ethylquinoline* which crystallised from alcohol in stout prisms, m. p. 132—133° (Found: N, 9·0; Cl, 22·4. $C_{17}H_{14}N_2Cl_2$ requires N, 8·8; Cl, 22·4%).

2-Amino-4-γ-diethylaminopropylaminoquinoline (VI; R = NH_2, R′ = NH·$[CH_2]_3$·NEt_2).—Ammonia was passed through a solution of 2-chloro-4-γ-diethylaminopropylaminoquinoline (5·2 g.) in phenol (20 g.) at 170—180° for 18 hours. The cooled mixture was treated with aqueous sodium hydroxide and ether, and the ether layer washed thoroughly with dilute sodium hydroxide and then with water and dried (Na_2SO_4). Removal of the solvent left a syrup which solidified on trituration with light petroleum (b. p. 60—80°). By crystallisation from benzene–light petroleum the *amino*-compound was obtained as colourless stout prisms, m. p. 125—126° (Found: N, 20·0. $C_{16}H_{24}N_4$ requires N, 20·6%).

2-p-Chlorophenylthioureido-4-γ-diethylaminopropylaminoquinoline (X; R = $[CH_2]_3$·NEt_2).—2-Amino-4-γ-diethylaminopropylaminoquinoline (13·5 g.), *p*-chlorophenyl *iso*thiocyanate (9·0 g.), and dry xylene (30 c.c.) were refluxed for 1 hour. On cooling, the clear solution deposited crystals which were filtered off, washed with benzene, and dried. Crystallisation from xylene gave pale yellow stout prisms (yield, 72%), m. p. 188—189° (Found: N, 15·4; S, 6·9. $C_{23}H_{31}N_5ClS$ requires N, 15·9; S, 7·25%).

2-p-Chlorophenylguanidino-4-γ-diethylaminopropylaminoquinoline (XI; R = $[CH_2]_3$·NEt_2).—The above thioureido-compound (6·5 g.) was stirred with saturated alcoholic ammonia (100 c.c.) and mercuric oxide (7 g.) for 24 hours at 30—35° with the continuous passage of ammonia into the solution. After cooling, the mixture was filtered and the dried residue extracted with hot xylene from which the product separated on cooling (yield, 78%). It formed colourless needles from xylene, m. p. 208° (Found: C, 65·3; H, 6·5; N, 19·8. $C_{23}H_{29}N_6Cl$ requires C, 65·0; H, 6·8; N, 19·8%). 2-p-*Chlorophenylguanidino-4-γ-diethylaminopropylaminoquinoline* is only very sparingly soluble in alcohol.

2-Amino-4-β-diethylaminoethylaminoquinoline (VI; R = NH_2, R′ = NH·$[CH_2]_2$·NEt_2.—Ammonia was passed for 22 hours into a solution of 2-chloro-4-β-diethylaminoethylaminoquinoline (21·9 g.) in phenol (50 g.) at 170—180°. The mixture was cooled, treated with sodium hydroxide solution, and shaken with ether. The ether solution after being washed with sodium hydroxide and then with water was extracted with 5% acetic acid. Addition of ammonia to this extract to render it alkaline to Brilliant-yellow precipitated *4-β-diethylaminoethylamino-2-phenoxyquinoline* (VI; R = OPh, R′ = NH·$[CH_2]_2$·NEt_2) as an oil which rapidly solidified. After being collected and dried, it crystallised from *cyclo*hexane in large irregular prisms, m. p. 104—105° (Found: N, 12·9. $C_{21}H_{25}ON_3$ requires N, 12·5%). Addition of sodium hydroxide to the aqueous filtrate precipitated *2-amino-4-β-diethylaminoethylaminoquinoline* as an oil which gradually solidified (yield, 13 g.). After drying, it crystallised from *cyclo*hexane with the addition of a little water as practically colourless laminæ, m. p. 114—115° (Found: C, 69·8; H, 8·7; N, 21·8. $C_{15}H_{22}N_4$ requires C, 69·75; H, 8·5; N, 21·75%). Under the above conditions of crystallisation it was sometimes obtained as a *hydrate*, m. p. 75—77° (Found: C, 63·2; H, 8·8; N, 18·9. $C_{15}H_{22}N_4,1·5H_2O$ requires C, 63·2; H, 8·8; N, 19·6%).

2-p-Chlorophenylthioureido-4-β-diethylaminoethylaminoquinoline (X· R = $[CH_2]_2$·NEt_2), prepared by heating the above amino-compound (10 g.) with *p*-chlorophenyl *iso*thiocyanate (6·6 g.) in boiling xylene (30 c.c.) for 1 hour, crystallised from benzene in colourless needles, m. p. 181—182° (Found: N, 16·3; S, 7·2. $C_{22}H_{26}N_5ClS$ requires N, 16·4; S, 7·5%).

2-p-Chlorophenylguanidino-4-β-diethylaminoethylaminoquinoline (XI; R = $[CH_2]_2$·NEt_2):—The preceding thiourea (6 g.) and mercuric oxide (6 g.) were added to saturated alcoholic ammonia (100 c.c.) at 0°. With stirring, the mixture was allowed to regain room temperature, then warmed to 30—35° and ammonia passed in for 2 hours. After being stirred at this temperature for 19 hours the mixture was filtered and the insoluble residue dried and extracted with benzene to give the *product* as colourless needles, m. p. 202—203° (Found: N, 20·2. $C_{22}H_{27}N_6Cl$ requires N, 20·5%).

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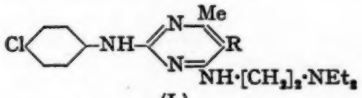
168. *Synthetic Antimalarials. Part XVIII. 3-Dialkylaminoalkylaminodiphenylamines.*

By Frederick G. Mann and J. W. Geoffrey Porter.

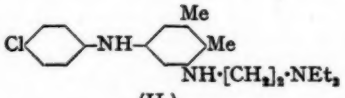
In order to determine whether the antimalarial activity of certain 2-anilino-4-dialkylaminoalkylaminopyrimidines of type (I) was determined primarily by their general structure, the corresponding compounds in which the pyrimidine ring has been replaced by a benzene ring, *i.e.*, diphenylamines of type (II), have been synthesised. The similar benzene analogues of the active 2-amino-4-dialkylaminoalkylaminopyrimidines of type (III) have also been synthesised.

All these benzene analogues proved to be devoid of antimalarial activity, however, and the activity of both the above types of pyrimidine compound must therefore be intimately associated either with the pyrimidine ring itself or with the tautomerism which this ring allows.

When this investigation was started, it was known that 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I, R = H) showed marked antimalarial activity against avian malaria; the corresponding *p*-methoxyanilino-compound showed lower activity, but the 5 : 6-dimethyl homologue (I, R = Me) an activity slightly greater than that of (I, R = H) (Curd and Rose, *J.*, 1945, **343**; Curd, Richardson, and Rose, *ibid.*, p. 378). Many other homologues, having similar 4-dialkylaminoalkylamino-substituents, also showed varying degrees of activity.



(I.)



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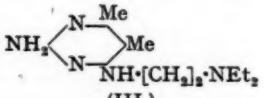


(III.)

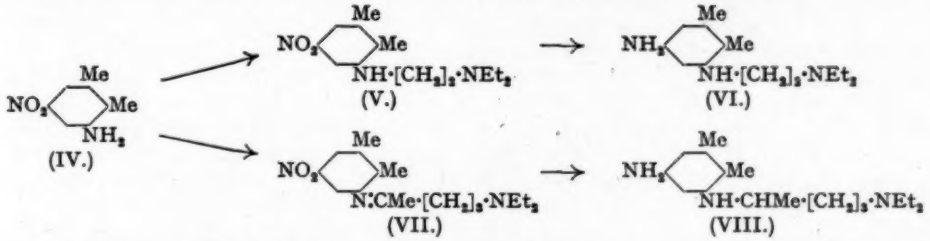
It had been suggested (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 157; Curd, Davis, and Rose, *J.*, 1946, 351) that these various anilino-pyrimidines might owe their antimalarial activity to their interference with some essential metabolic process involving riboflavin, due to the structural similarity which not only exists between riboflavin and the pyrimidines themselves, but might also exist between riboflavin and the most probable degradation products of these pyrimidines, for example, the corresponding 4-hydroxy-pyrimidines which could be formed by hydrolytic removal of the alkylamino-group from the drug. It was shown later by Madinaveitia (*Biochem. J.*, in the press) that the growth-inhibitory action of the above pyrimidines, as well as that of mepacrine and quinine, for *Lactobacillus casei* was actually antagonised by riboflavin.

It became of interest therefore to prepare diphenylamine compounds of type (II), which differed from compounds of type (I) only in that the pyrimidine ring of the latter had now been replaced by a benzene ring. If antimalarial activity is due primarily to a general structural similarity between riboflavin and the drug, compounds of type (II) should have an activity of the same order as that of their analogues of type (I); if, however, it is due primarily to a structural similarity between riboflavin and the main degradation products of the drug, then compounds of type (II), by virtue of their greater stability, might well prove inactive.

It should be noted, however, that a further factor enters here which might itself largely offset the result of any general structural similarity between the two classes of drugs. Pyrimidines of type (I) can clearly exist in several tautomeric forms (formulated in Part VIII, *J.*, 1946, 713), whereas in the benzene analogues of type (II) no such tautomerism can occur. It is noteworthy that a similar tautomerism can occur in mepacrine, and Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) has suggested that the antimalarial activity of mepacrine is closely associated with this tautomerism.

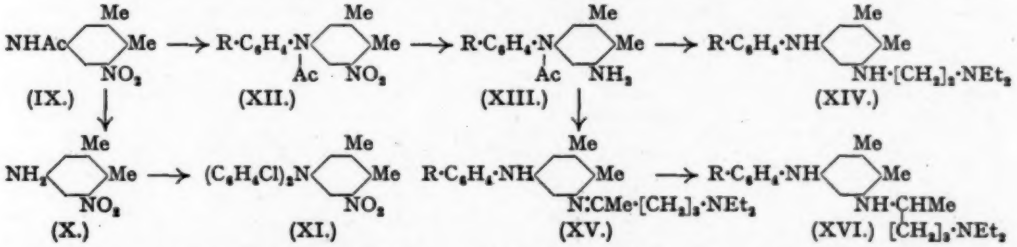
It is clear, however, that even if this structural-similarity factor is the underlying cause of the antimalarial activity of certain types of drug, it cannot apply to all types. For example, Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1945, 357) have shown that 2-amino-4-β-diethylaminoethylamino-5 : 6-dimethylpyrimidine (III), which does not show this structural similarity with riboflavin, has an activity of approximately the same value as that of (I, R = Me). It is significant that Madinaveitia (*loc. cit.*) has found that the action of pyrimidines of type (III) is not antagonised by riboflavin. The additional object of the present investigation therefore was to prepare the benzene analogues of (III), in order to determine whether in this class of drug also the pyrimidine ring, with its accompanying tautomerism, was essential for antimalarial activity. The synthesis of these simpler monocyclic compounds is conveniently described before that of the more complex diphenylamine derivatives.

Condensation of 5-nitro-3-amino-*o*-xylene (IV) with β-diethylaminoethyl chloride furnished the *hydrochloride* of *5-nitro-3-β-diethylaminoethylamino-o-xylene* (V). Catalytic reduction followed by basification then gave *5-amino-3-β-diethylaminoethylamino-o-xylene* (VI). Many



attempts were then made to condense the amine (IV) with δ-bromo-α-diethylamino-*n*-pentane, $CHMeBr·[CH_2]_3·NEt_2$, in order ultimately to make (VIII), *i.e.*, the analogue of (VI) containing the basic side chain of mepacrine. All such attempts failed, however, in spite of a variety of conditions employed. Ultimately success was achieved by utilising the method developed by Ashley and Grove (*J.*, 1945, 768) for introducing this side chain into the aminopyridines. For this purpose, methyl 3-diethylamino-*n*-propyl ketone was converted into the diethyl ketal, $CMe(OEt)_2·[CH_2]_3·NEt_2$, which was readily condensed with the amine (IV) to give the anil (VII). This compound on catalytic reduction furnished *5-amino-3-δ-diethylamino-α-methyl-n-butylamino-o-xylene* (VIII).

For the preparation of the corresponding diphenylamines, 4-amino-*o*-xylene was acetylated and then nitrated to furnish 3-nitro-5-acetamido-*o*-xylene (IX) (cf. Crossley and Morrell, *J.*, 1911, **99**, 2350), hydrolysis then giving 3-nitro-5-amino-*o*-xylene (X). This amine was subjected to an Ullmann condensation with *p*-chloroiodobenzene in the presence of copper, but



in spite of a wide variety of conditions the main product isolated was always *4′ : 4″-dichloro-3-nitro-4 : 5-dimethyltriphenylamine* (XI), and it was clear that the initial production of the diphenylamine must have been a slow process compared with its conversion into the triphenylamine derivative. It should be noted that this preferential formation of a tertiary amine by the Ullmann reaction is rare but not unique: Wibaut and La Bastide (*Rec. Trav. chim.*, 1933, **52**, 493) have shown that 2-iodopyridine and 2-aminopyridine, when heated with potassium carbonate and copper, furnish the tri-2-pyridylamine.

This difficulty was overcome by employing the acetamido-compound (IX), which in the presence of copper bronze and potassium iodide readily combined with *p*-chloroiodobenzene to form *4′-chloro-3-nitro-N-aceto-4 : 5-dimethyldiphenylamide* (XII, R = *p*-Cl). The latter was then reduced to the *3-amino*-derivative (XIII, R = Cl) which, after condensation with β-2-diethylaminoethyl chloride and subsequent hydrolysis, furnished *4′-chloro-3-β-diethylaminoethylamino-4 : 5-dimethyldiphenylamine* (XIV, R = Cl).

When the acetyl group in (XIII) was removed, the resulting *amine* readily condensed with the above diethyl ketal to give the anil (XV, R = Cl), which on catalytic reduction gave *4′-chloro-3-(δ-diethylamino-α-methyl-n-butylamino)-4 : 5-dimethyldiphenylamine* (XVI, R = Cl).

Attempts were then made to prepare compounds of type (XIV) and (XVI) in which R = *p*-MeO, as this group has considerable significance in many antimalarial compounds. *p*-Bromoanisole was successfully condensed with the acetamido-compound (IX), but the acetodiphenylamide could not readily be isolated: consequently the crude product was hydrolysed and the pure *3-nitro-4′-methoxy-4 : 5-dimethyldiphenylamine* thus obtained. This compound was reduced to the *3-amino*-derivative, which condensed with β-diethylaminoethyl chloride to give *3-β-diethylaminoethylamino-4′-methoxy-4 : 5-dimethyldiphenylamine* (XIV,

R = MeO). The 3-amino-derivative also gave the anil (XV, R = MeO) which on hydrogenation furnished *3-δ-diethylamino-α-methyl*-n-*butylamino-4'-methoxy*-**4 : 5-*dimethyldiphenylamine*** (XVI, R = MeO). It should be noted that, whereas the constitution of the last compound is beyond doubt, that of (XIV, R = MeO) is not absolutely certain, since the ethyl chloride might conceivably condense with the secondary amino-group : the reactivity of the 3-amino-group is so very much greater, however, that this possibility can be ignored.

The two xylene derivatives (VI) and (VIII) and the four diphenylamine derivatives (XIV, R = Cl and MeO) and (XVI, R = Cl and MeO) have been tested against *P. gallinaceum* in chicks and found to be inactive not only against the blood forms but also prophylactically. It is clear, therefore, that the marked antimalarial activity of the two types of pyrimidine derivative (I) and (III) must be intimately associated either with the pyrimidine ring as such, or with the tautomerism which this ring allows, and that a superficial structural similarity with riboflavin which ignores this tautomerism, as in the diphenylamine derivatives, is insufficient to produce activity.

Experimental.

5-Nitro-3-amino-o-xylene (IV). This compound, prepared according to Noelting, Braun, and Thesmar (*Ber.*, 1901, **34**, 2242), was obtained in 35% yield as yellow needles, m. p. 111—112°.

5-Nitro-3-β-diethylaminoethylamino-o-xylene (V).—A solution of 5-nitro-3-amino-*o*-xylene (12 g.) in xylene (50 c.c.) was refluxed with 2-diethylaminoethyl chloride (45 c.c. of a 30% xylene solution; 1·1 mols.) for 4 hours. On cooling, the product, which had separated during the heating, solidified; it was collected, and recrystallised from ethyl alcohol–petrol (equal vols., 400 c.c.), furnishing pale yellow plates of the *hydrochloride* of the diethylamino-compound (V), m. p. 182—183° (Found : C, 55·8; H, 8·1. $C_{14}H_{23}O_2N_3$,HCl requires C, 55·7; H, 8·0%) (15 g., 70%). This compound formed a *picrate*, yellow needles from aqueous acetone containing a slight excess of picric acid, m. p. 164—165° (Found : C, 48·3; H, 5·5. $C_{14}H_{23}O_2N_3$,$C_6H_3O_7N_3$ requires C, 48·5; H, 5·3%).

5-Amino-3-β-diethylaminoethylamino-o-xylene (VI) (6048).—A solution of the above hydrochloride (9 g.) in 95% ethyl alcohol (150 c.c.) was rapidly hydrogenated in the presence of Adams's platinum catalyst (0·2 g.) at room temperature and pressure. The filtered solution was evaporated to dryness under reduced pressure, and the deliquescent crystalline residue dissolved in water and basified with aqueous sodium carbonate. The crude *5-amino*-compound (VI) which separated was collected, dried, and crystallised from petrol (b. p. 40—60°); colourless needles, m. p. 75—76° (Found : C, 71·5; H, 10·4; N, 18·0. $C_{14}H_{25}N_3$ requires C, 71·5; H, 10·6; N, 17·9%).

When dry hydrogen chloride was passed into a solution of the amine in warm petrol, the deliquescent *trihydrochloride* rapidly crystallised, m. p. 170° (decomp.) (Found : N, 12·25. $C_{14}H_{28}N_3$,3HCl requires N, 12·2%). When the amine was refluxed with acetic acid–acetic anhydride, and the product poured into water and basified with sodium carbonate, the *diacetyl* derivative slowly crystallised; needles from very dilute aqueous alcohol, m. p. 140—141° (Found : C, 67·2; H, 9·4; N, 13·0. $C_{18}H_{29}O_2N_3$ requires C, 67·6; H, 9·1; N, 13·1%).

α-Diethylamino-n-pentan-δ-one Diethyl Ketal (cf. van Schelven, B.P. 388,087).—A solution of the amino-ketone (90 g.) in a slight excess of dilute hydrochloric acid was evaporated to dryness under reduced pressure, the residual hydrochloride dissolved in alcohol (100 c.c.) containing dry hydrogen chloride (1 g.), ethyl orthoformate (100 g., 1·2 mols.) added, and the mixture set aside for 8 days. The solution was then partly neutralised by addition of sodium ethoxide (from 12 g. of sodium), filtered from sodium chloride, and shaken with an excess of silver oxide. The filtered solution was fractionally distilled, and the ketal obtained as a colourless liquid, b. p. 116—118°/14 mm. (110 g., 85%).

5-Amino-3-(δ-diethylamino-α-methyl-n-butylamino)-o-xylene (VIII) (6049).—A mixture of the 5-nitro-compound (IV) (10 g.), the diethyl ketal (15·5 g., 1·1 mols.), and ammonium chloride (0·05 g.) was heated in a small distilling flask by means of a metal-bath. As the temperature reached 160° a brisk reaction set in with evolution of ethyl alcohol; when this subsided the temperature was increased to 210° and maintained there for 0·5 hour. The excess of ketal was removed under reduced pressure, and the residual anil dissolved in ethyl alcohol (100 c.c.) and hydrogenated in the presence of Adams's catalyst (0·2 g.) at 60° under a pressure of 90 atm., the almost theoretical absorption of hydrogen (4 mols.) taking 4 hours. The alcohol was then evaporated from the filtered solution, the residue refluxed with 15% hydrochloric acid (60 c.c.) for 1 hour to hydrolyse any traces of unchanged anil, and the solution cooled, basified with sodium carbonate, and extracted with ether, dried, and distilled. A small initial fraction of 3 : 5-diamino-*o*-xylene, b. p. 130°/0·05 mm., was followed by the main fraction, b. p. 170—175°/0·05 mm. This on redistillation gave the *amine* (VIII) as a pale brown syrup, b. p. 172—174°/0·01 mm. (Found : C, 73·3; H, 11·6; N, 15·3. $C_{17}H_{31}N_3$ requires C, 73·6; H, 11·2; N, 15·2%). The amine slowly darkens on exposure to light. No crystalline salts could be obtained; those prepared were all intractable gums which rapidly darkened when exposed to light.

4-Acetamido-o-xylene.—A solution of 4-amino-*o*-xylene (50 g.) in cold acetic acid (50 c.c.) was diluted with water (200 c.c.) and continuously agitated whilst acetic anhydride (50 g., 1·1 mols.) was slowly added. The acetamido-compound readily crystallised and, after the product had been poured into water (2 l.), was collected, washed and dried; m. p. 94—95° (65 g., 97%). Jacobsen (*Ber.*, 1884, **17**, 161) acetylated the amine both with acetic acid alone and with acetic acid–acetyl chloride; we find that the use of acetic acid–acetic anhydride gives a syrupy product containing much diacetyl derivative.

3-Nitro-5-acetamido-o-xylene (IX).—Crossley and Morrell (*loc. cit.*) give no detailed directions for this preparation. The previous compound (100 g.) was added with stirring to concentrated sulphuric acid (500 c.c.) maintained at − 10°, and the resulting solution continuously stirred and kept below − 7° whilst a solution of nitric acid (40 c.c., *d* 1·42, 1·05 mols.) in concentrated sulphuric acid (100 c.c.) was

slowly added. The product was poured on crushed ice (*ca.* 10 kg.), and the solid nitro-compound collected, washed with water, and dried. Recrystallisation from alcohol gave colourless needles, m. p. 207—208° (Found: C, 58·0; H, 6·1. Calc. for $C_{10}H_{12}O_3N_2$: C, 57·7; H, 5·8%).

3-Nitro-5-amino-o-xylene (X).—The acetyl compound was refluxed with 70% sulphuric acid (5 parts) for 30 minutes, and the solution poured on ice and made alkaline with ammonia. The precipitated 5-amino-compound, collected and recrystallised from aqueous alcohol, gave deep orange needles, m. p. 74—75° (Found: C, 57·8; H, 5·9. Calc. for $C_8H_{10}O_2N_2$: C, 57·9; H, 6·0%). This compound has previously been prepared only by the reduction of the 3 : 5-dinitro-derivative (Noelting *et al.*, *loc. cit.*).

4′ : 4″-Dichloro-3-nitro-4 : 5-dimethyltriphenylamine (XI).—A mixture of 3-nitro-5-amino-*o*-xylene (X) (10·5 g.), *p*-chloroiodobenzene (16 g., 1·1 mols.), anhydrous potassium carbonate (5 g., 1·2 mols.), copper powder (0·2 g.), potassium iodide (0·05 g.), and dry nitrobenzene (50 c.c.) was gently refluxed with occasional shaking for 7 hours. The product was steam-distilled to remove nitrobenzene and *p*-chloroiodobenzene, and the tarry residue dried and extracted (Soxhlet) with petrol (b. p. 40—60°; 250 c.c.). The extract on cooling deposited a reddish-yellow solid, which on crystallisation from alcohol furnished the *triphenylamine* (XI), pale yellow crystals, m. p. 146—147° (Found: N, 7·3; Cl, 18·1. $C_{20}H_{16}O_2N_2Cl_2$ requires N, 7·2; Cl, 18·3%) (5 g., 20%).

Aqueous dilution of the alcoholic mother-liquor precipitated a red solid, which, crystallised from methyl alcohol, furnished 4′-chloro-3-nitro-4 : 5-dimethyldiphenylamine (see later); m. p. 120—121°. Similar dilution of the methyl-alcoholic mother-liquor gave unchanged (X) (1·5 g.).

4′-Chloro-3-nitro-N-aceto-4 : 5-dimethyldiphenylamide (XII, R = Cl).—A mixture of (IX) (30 g.), *p*-chloroiodobenzene (170 g.), anhydrous potassium carbonate (15 g.), copper powder (1 g.), and potassium iodide (0·5 g.) was heated with continuous stirring in a metal-bath at 240° for 4 hours. The cool product was poured into petrol (b. p. 60—80°, 1 l.), and the mixture boiled, filtered, and cooled. The *acetodiphenylamide* (XII, R = Cl) which separated was once recrystallised from petrol; pale yellow needles, m. p. 121—122° (Found: C, 60·7; H, 4·8; N, 8·9. $C_{16}H_{15}O_3N_2Cl$ requires C, 60·3; H, 4·7; N, 8·8%) (30 g., 70%).

4′-Chloro-3-nitro-4 : 5-dimethyldiphenylamine.—The previous compound was refluxed with 70% sulphuric acid (10 parts) for 30 minutes, and the solution cooled, poured into water, and basified with ammonia. The precipitated *diphenylamine* was collected and recrystallised from methyl alcohol; orange-red needles, m. p. 121—122° (Found: C, 61·2; H, 4·7; N, 10·3. $C_{14}H_{13}O_2N_2Cl$ requires C, 60·8; H, 4·7; N, 10·1%).

4′-Chloro-3-amino-N-aceto-4 : 5-dimethyldiphenylamide (XIII, R = Cl).—A solution of (XII, R = Cl) (15·5 g.) in alcohol (250 c.c.) was hydrogenated (Adams's catalyst, 0·2 g.) at 50° and 50 atm., theoretical absorption occurring in 3 hours. The filtered solution was evaporated under reduced pressure, and the crystalline residue extracted (Soxhlet) with petrol (b. p. 60—80°, 1 l.). The *acetamide* (XIII, R = Cl) separated from the extract as colourless crystals, m. p. 118—119° (Found: C, 66·4; H, 6·2. $C_{16}H_{17}ON_2Cl$ requires C, 66·5; H, 5·9%). When hydrogen chloride was passed into an ethereal solution of this amine, the *hydrochloride* readily crystallised, m. p. 210—212° (decomp.) (Found: C, 58·6; H, 5·7; N, 8·3. $C_{16}H_{17}ON_2Cl,HCl$ requires C, 59·0; H, 5·7; N, 8·6%). The amine also readily afforded a *picrate*, yellow needles from aqueous alcohol, m. p. 198—199° (decomp.) (Found: C, 51·2; H, 4·2. $C_{16}H_{17}ON_2Cl,C_6H_3O_7N_3$ requires C, 51·0; H, 3·9%).

When the amine was refluxed with dilute hydrochloric acid, the *hydrochloride* of *4′-chloro-3-amino-4 : 5-dimethyldiphenylamine* (6050) separated during the heating in almost theoretical yield; pale pink needles from aqueous alcohol, m. p. 236—237° (decomp.) (Found: C, 59·5; H, 5·8; N, 9·8. $C_{14}H_{15}N_2Cl,HCl$ requires C, 59·3; H, 5·6; N, 9·9%). Addition of aqueous ammonia to a warm aqueous-alcoholic solution of the hydrochloride precipitated the free *amine*, colourless needles from petrol, m. p. 98—99° (Found: C, 67·6; H, 6·1; N, 11·4. $C_{14}H_{13}N_2Cl$ requires C, 68·1; H, 6·1; N, 11·3%).

When the acetyl derivative (XIII) was hydrolysed with 70% sulphuric acid and the resulting solution poured into water, the *sulphate monohydrate* separated; colourless needles from alcohol, m. p. 173—174° [Found: C, 55·1; H, 5·6; N, 9·2. $(C_{14}H_{15}N_2Cl)_2,H_2SO_4,H_2O$ requires C, 55·1; H, 5·9; N, 8·8%]. The yield, however, was now only 40%.

4′-Chloro-3-β-diethylaminoethylamino-4 : 5-dimethyldiphenylamine (XIV, R = Cl) (6051).—A solution of (XIII, R = Cl) (6 g.) in xylene and a solution of β-diethylaminoethyl chloride (1·1 mols.) in xylene (14 c.c., of 30% concentration) were refluxed together for 12 hours, the condensation product separating meanwhile as a heavy oil. The cold mixture was then extracted with 10% aqueous hydrochloric acid (50 c.c.), and the extract refluxed for 1 hour to hydrolyse the acetamido-group. The cold extract was basified with ammonia, the oily deposit extracted with ether, and the dried ethereal extract then distilled. The *diphenylamine* (XIV, R = Cl) was obtained as a viscous syrup, b. p. 222—223°/0·002 mm. (Found: C, 70·0; H, 8·4; N, 12·4. $C_{20}H_{25}N_3Cl$ requires C, 69·5; H, 8·1; N, 12·15%) (5 g., 70%).

When acetone solutions of this amine and of *p*-toluenesulphonic acid were mixed, the *di-p-toluenesulphonate* crystallised, m. p. 201° (preliminary softening and darkening) (Found: C, 58·9; H, 6·5; N, 6·1. $C_{20}H_{25}N_3Cl,2C_7H_8O_3S$ requires C, 59·2; H, 6·4; N, 6·1%). This was the only crystalline salt of the base isolated.

4′-Chloro-3-(δ-diethylamino-α-methyl-n-butylamino)-4 : 5-dimethyldiphenylamine (XVI, R = Cl) (6052).—4′-Chloro-3-amino-4 : 5-dimethyldiphenylamine (11 g.), the diethyl ketal (12 g., 1·1 mols.), and ammonium chloride (0·05 g.) were heated together for 2 hours, initially at 170° and later at 210°. The excess of ketal was removed under reduced pressure, and the residual anil dissolved in alcohol (70 c.c.) and hydrogenated (Adams's catalyst, 0·2 g.) at 60° and 100 atm. for 3 hours. The alcohol was then evaporated from the cold filtered solution, and the residue refluxed with 15% hydrochloric acid (60 c.c.) for 1 hour. The cold solution was basified (sodium hydroxide), extracted with ether, and the dried extract then distilled; the *diphenylamine* (XVI, R = Cl) was obtained as a pale yellow oil, b. p. 240—242°/0·07 mm. (Found: C, 71·4; H, 8·8; N, 11·0; Cl, 9·2. $C_{22}H_{34}N_3Cl$ requires C, 71·2; H, 8·8; N, 10·8; Cl, 9·2%). No crystalline salts of this amine could be isolated.

3-*Nitro*-4′-*methoxy*-4 : 5-*dimethyldiphenylamine*.—A mixture of (IX) (35 g.), *p*-bromoanisole (180 g.), potassium carbonate (17 g.), copper powder (1 g.), and potassium iodide (0·7 g.) was heated with stirring at 240° for 6 hours in an apparatus so arranged that water formed by slight decomposition could distil away. The cool product was then poured into hot petrol (b. p. 60—80°, 800 c.c.), and the mixture boiled, filtered, evaporated to *ca.* 250 c.c., and then steam-distilled until free from *p*-bromoanisole. The oily residue was then refluxed with 12% hydrochloric acid (120 c.c.) for 1 hour, cooled, and repeatedly extracted with ether until the extracts were colourless. The united, dried extracts on distillation gave the above *diphenylamine* as a viscous red syrup, b. p. 238—240°/0·01 mm. (30 g., 64%); trituration with methyl alcohol induced crystallisation, and the compound then crystallised from *cyclo*hexane in orange-yellow plates, m. p. 122—123° (Found: C, 66·5; H, 6·3; N, 10·1. $C_{15}H_{14}O_3N_2$ requires C, 66·2; H, 5·9; N, 10·3%).

3-*Amino*-4′-*methoxy*-4 : 5-*dimethyldiphenylamine* (6053).—A solution of the above compound (30 g.) in alcohol (250 c.c.) was hydrogenated as usual at 50° and 50 atm. for 5 hours. Fractional distillation ultimately gave this *diphenylamine* as a colourless oil, b. p. 220°/0·01 mm., which set to a brittle deliquescent glass, which could not be crystallised (Found: N, 11·3. $C_{15}H_{16}ON_2$ requires N, 11·6%) (22 g., 87%). This compound formed a *picrate* which, recrystallised from very dilute aqueous picric acid, formed fine yellow needles, m. p. 183° (decomp.) (Found: C, 53·25; H, 4·7. $C_{15}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 53·5; H, 4·5%).

3-β-*Diethylaminoethylamino*-4′-*methoxy*-4 : 5-*dimethyldiphenylamine* (XIV, R = MeO) (6054).—This was prepared precisely similarly to the 4′-chloro-analogue but by using the unacetylated diphenylamine, and obtained initially as a crude fraction, b. p. 235—240°/0·06 mm., which on refractionation gave the pure *diphenylamine* as a colourless oil, b. p. 238°/0·01 mm. (Found: N, 12·6. $C_{21}H_{31}ON_3$ requires N, 12·3%) (60%).

3-δ-*Diethylamino*-α-*methyl*-n-*butylamino*-4′-*methoxy*-4 : 5-*dimethyldiphenylamine* (XVI, R = MeO) (6055).—This *compound* was also prepared precisely similarly to the 4′-chloro-analogue and obtained as a pale green oil, b. p. 210°/0·002 mm. (Found: C, 74·8; H, 9·3; N, 11·3. $C_{24}H_{37}ON_3$ requires C, 75·2; H, 9·7; N, 11·0%): 58% of the theoretical.

No crystalline salts of the last two amines could be isolated.

This research was carried out on behalf of the Medical Research Council under a wartime collaborative agreement on antimalarial research between the Medical Research Council and Imperial Chemical Industries Ltd. We are greatly indebted to the Council for a grant (J. W. G. P.) and to Imperial Chemical Industries Ltd. both for materials and for carrying out the antimalarial tests.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 30th*, 1946.]

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169. *Synthetic Antimalarials. Part XIX. Dialkylaminoalkylaminodiphenylguanidines.*

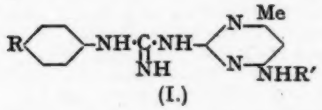
By FREDERICK G. MANN, FREDERICK T. NAYLOR, and J. W. GEOFFREY PORTER.

The study of the effect on antimalarial activity caused by replacing the pyrimidine by the benzene ring has been extended to include the diphenylguanidines of types (II) and (III), the former being the benzene analogues of the active 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines of type (I).

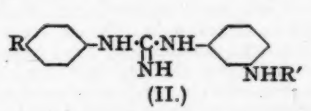
The scope of the investigation was restricted by the intractable nature of many of the products.

IN Part XVIII (Mann and Porter, preceding paper) an attempt was made to ascertain whether the marked antimalarial properties of the 2-*p*-chloroanilino-4-dialkylaminoalkylamino-6-methylpyrimidines were determined primarily by their general molecular structure, or more specifically by the presence and properties of the constituent pyrimidine ring. This factor was investigated by preparing analogous compounds differing only in that the pyrimidine ring of the former compounds had now been replaced by a benzene ring. The compounds so prepared, of the general type 4′-chloro-3-dialkylaminoalkylamino-4 : 5-dimethyldiphenylamine, were found to be without antimalarial activity.

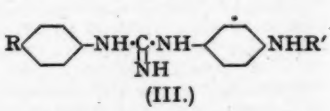
It was clearly desirable, however, that the evidence concerning this factor should not be limited to one class of pyrimidine derivative. The 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines (Curd and Rose, *J.*, 1946, 362) (I) constitute a second class of pyrimidine derivative having high antimalarial activity, and it was considered of interest,



(I.)



(II.)

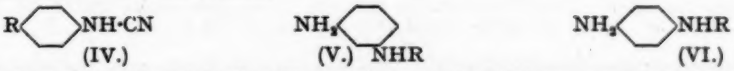


(III.)

therefore, to prepare their benzene analogues, *i.e.*, diphenylguanidines of type (II). Furthermore, in order to determine whether the position of the dialkylaminoalkylamino-

substituent relative to that of the guanidine nucleus has any marked influence on the antimalarial activity, the preparation of the *pp'*-disubstituted diphenylguanidines of type (III) was investigated.

The most convenient method for the preparation of asymmetrically disubstituted diaryl guanidines is the interaction of an aryl cyanamide with the hydrochloride of an arylamine (Heller and Bauer, *J. pr. Chem.*, 1902, **65**, 384). Thus *p*-chlorophenylcyanamide (IV, R = Cl) condensed with N-β-*diethylaminoethyl*-m-*phenylenediamine* (V, R = $CH_2 \cdot CH_2 \cdot NEt_2$) in alcoholic hydrogen chloride to afford N-p-*chlorophenyl*-N'-m-β-*diethylaminoethylaminophenylguanidine* (II, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$) in moderate yield. A similar condensation between (IV, R = Cl) and N-β-*diethylaminoethyl*-p-*phenylenediamine* furnished N-p-*chlorophenyl*-N'-p-β-*diethylaminoethylaminophenylguanidine* (III, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$). Both the above guanidines were crystalline compounds.



(IV.) (V.) (VI.)

N-β-Diethylaminoethyl-*m*-phenylenediamine has previously been prepared (U.S.P. 1,757,394) by heating *m*-phenylenediamine with β-diethylaminoethyl chloride. A more convenient preparation both of this compound and of *N*-β-diethylaminoethyl-*p*-phenylenediamine consists in the condensation of β-diethylaminoethyl chloride and the corresponding nitroaniline to give the *hydrochloride* of 1-*nitro*-3-β-*diethylaminoethylamino*- and of 1-*nitro*-4-β-*diethylaminoethylamino-benzene*. Catalytic reduction of these hydrochlorides afforded good yields of the phenylenediamines (V and VI, R = $CH_2 \cdot CH_2 \cdot NEt_2$).

With the object of preparing the analogous guanidines carrying the δ-diethylamino-α-methyl-*n*-butyl side chain, N-δ-*diethylamino*-α-*methyl*-n-*butyl*-m- and -p-*phenylenediamine* (V and VI, R = $CHMe \cdot [CH_2]_3 \cdot NEt_2$) were prepared by condensing the appropriate nitroaniline with 5-diethylamino-*n*-pentan-2-one diethyl ketal and reducing the resulting anil to give the required product (cf. Mann and Porter, *loc. cit.*). Although both these substituted phenylenediamines appeared to react with (IV, R = Cl) under the usual conditions, the products proved to be intractable, deliquescent gums which could neither by crystallised nor induced to give crystalline salts. Dewar (*J.*, 1944, 534) has noted similar difficulties in attempting to crystallise *N*-dialkylaminoalkyldiarylguanidines.

Attempts were next made to prepare compounds of types (II) and (III) in which R = OMe. *p*-Methoxyphenylthiourea (Dienske, *Rec. Trav. chim.*, 1931, **50**, 407) was treated with lead hydroxide to give p-*methoxyphenylcyanamide* (IV, R = OMe). This reacted normally with each of the above four substituted phenylenediamines but no crystalline product could be isolated. Analysis of the resinous gum produced by the reaction between (IV, R = OMe) and *N*-β-diethylaminoethyl-*p*-phenylenediamine showed it to be almost certainly the required N-p-*methoxyphenyl*-N'-p-β-*diethylaminoethylaminophenylguanidine* (III, R = OMe, R' = $CH_2 \cdot CH_2 \cdot NEt_2$).

An alternative synthetic route was equally unproductive of crystalline products. *p*-Methoxyphenylcyanamide was heated in alcoholic solution with *m*-nitroaniline hydrochloride to form N-p-*methoxyphenyl*-N'-m-*nitrophenylguanidine hydrochloride* which was catalytically reduced to N-p-*methoxyphenyl*-N'-m-*aminophenylguanidine hydrochloride* (II, R = OMe, R' = H). The latter compound, however, did not condense normally with β-diethylaminoethyl chloride: a complex mixture of products, arising apparently from the rupture of the guanidino-linkage, being isolated.

Only the two crystalline guanidine derivatives (II and III, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$) have been tested. Whereas the former (5220) showed significant activity (+ to ++ at 80 mg./kg.) the latter (6180) was inactive at the same dosage (highest tested). The former is the more closely related to the active 2-arylguanidino-4-dialkylaminoalkylaminopyrimidines of type (I), and the conclusion may therefore perhaps be drawn that the replacement of a pyrimidine ring by a benzene ring in an antimalarial structure based on pyrimidine does not necessarily lead to complete loss of activity despite the results given in the previous paper. In this connection it may be noted that, whereas the diphenylamines described in the previous paper do not retain any of the tautomeric possibilities characteristic of their pyrimidine analogues, the diphenylguanidine (II, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$) is not devoid of all the tautomeric possibilities existent in type (I).

Experimental.

1-*Nitro*-3-β-*diethylaminoethylaminobenzene*.—A mixture of *m*-nitroaniline (100 g.) and β-diethylaminoethyl chloride (105 g., 1·1 mols.) in xylene (500 c.c.) was refluxed for 3 hours. The crystalline

hydrochloride was then collected and recrystallised from ethyl alcohol–light petroleum (b. p. 60—80°) (equal vols.); pale yellow needles, m. p. 177—178° (Found: N, 15·3; Cl, 13·2. $C_{12}H_{19}O_2N_2$,HCl requires N, 15·4; Cl, 13·0%). Yield, 140 g.; 70%.

Basification of an aqueous solution of the hydrochloride furnished the oily *base* (Found: C, 60·35; H, 8·1; N, 17·7. $C_{12}H_{19}O_2N_2$ requires C, 60·7; H, 8·1; N, 17·7%). The base readily afforded a *picrate*, orange crystals from alcohol, m. p. 149—150° (Found: N, 18·2. $C_{12}H_{19}O_2N_2,C_6H_3O_7N_3$ requires N, 18·0%).

1-*Nitro*-4-*β-diethylaminoethylaminobenzene hydrochloride* was similarly prepared and recrystallised; yellow needles, m. p. 159—160° (Found: C, 52·35; H, 7·6; N, 15·3. $C_{12}H_{19}O_2N_2Cl$ requires C, 52·6; H, 7·6; N, 15·4%). Yield, 72%. The *picrate*, yellow needles from ethyl alcohol, had m. p. 168—169° (Found: N, 18·5. $C_{12}H_{19}O_2N_2,C_6H_3O_7N_3$ requires N, 18·0%).

N-*β-Diethylaminoethyl*-m-*phenylenediamine* (V, R = CH_2·CH_2·NEt_2).—A solution of 1-nitro-3-*β*-diethylaminoethylaminobenzene hydrochloride (140 g.) in 90% aqueous ethyl alcohol (350 c.c.) was hydrogenated (Adams's catalyst, 0·3 g.) at room temperature and atmospheric pressure. The filtered solution was evaporated and then basified with aqueous sodium hydroxide. The product was extracted with ether and the dried extract fractionally distilled. The pure *amine* had b. p. 154°/0·05 mm. (Found: C, 69·2; H, 10·4; N, 19·9. $C_{12}H_{21}N_3$ requires C, 69·5; H, 10·3; N, 20·3%). Yield, 106 g.; 85%.

N-*β-Diethylaminoethyl*-p-*phenylenediamine* (VI, R = CH_2·CH_2·NEt_2) was similarly prepared as a hygroscopic oil, b. p. 156°/0·02 mm. (Found: C, 69·1; H, 10·8; N, 21·0%).

p-*Chlorophenylcyanamide* (IV, R = Cl).—This compound was prepared from *p*-chlorophenylthiourea and obtained as colourless needles, m. p. 103° (Found: N, 18·4. Calc. for $C_7H_5N_2Cl$: N, 18·3%).

N-p-*Chlorophenyl*-N′-m-*β-diethylaminoethylaminophenylguanidine* (II, R = Cl, R′ = CH_2·CH_2·NEt_2).—A solution of (IV, R = Cl) (10 g.) and *N-β*-diethylamino-*m*-phenylenediamine (13 g., 1 mol.) in ethyl alcohol (50 c.c.) containing hydrogen chloride (2·5 g., 2 mols.) was refluxed for 20 hours. The whole was then poured into 5% acetic acid (300 c.c.) and filtered, and the filtrate was slowly run into an excess of ice-cold 10% aqueous sodium hydroxide. The sticky white solid which separated was collected and dried. Prolonged extraction (Soxhlet) with light petroleum (b. p. 60—80°) afforded the crude product, which readily separated from the hot solution. Recrystallisation from light petroleum gave the pure *guanidine*, m. p. 112—113° (Found: C, 63·8; H, 6·9; N, 19·5. $C_{19}H_{26}N_5Cl$ requires C, 63·4; H, 7·3; N, 19·5%). Yield, 3·8 g.; 17%.

N-p-*Chlorophenyl*-N′-p-*β-diethylaminoethylaminophenylguanidine* (III, R = Cl, R′ = CH_2·CH_2·NEt_2).—A solution of (IV, R = Cl) (11·8 g.) and *N-β*-diethylamino-*p*-phenylenediamine (16·4 g., 1 mol.) in ethyl alcohol (55 c.c.) containing hydrogen chloride (2·85 g., 2 mols.) was refluxed for 24 hours. The solution was then evaporated and the residue was triturated with a slight excess of 5% aqueous ammonia. The resulting gum was washed by stirring with water and dried. Repeated extraction with light petroleum (b. p. 40—60°) afforded the *guanidine* which was once recrystallised from light petroleum; colourless plates, m. p. 102—103° (Found: C, 63·5; H, 7·5; N, 19·0%). Yield, 5 g.; 18%.

N-*δ-Diethylamino-α-methyl*-n-*butyl*-m-*phenylenediamine* (V, R = CHMe·$[CH_2]_3$·NEt_2).—*m*-Nitroaniline (50 g.), 5-diethylamino-*n*-pentan-2-one diethyl ketal (88 g.), and ammonium chloride (0·05 g.) were heated together for 2 hours, initially at 170° and later at 210°. The excess of ketal was removed under reduced pressure and the residual anil was dissolved in alcohol (200 c.c.) and hydrogenated (Adams's catalyst, 0·2 g.) at 60° and 100 atmospheres during 3 hours. The filtered solution was evaporated and the residue refluxed with 15% hydrochloric acid (400 c.c.) for ½ hour. The cold solution was basified (sodium hydroxide) and extracted with ether, and the dried extract was distilled. The *amine* was obtained as a colourless oil, b. p. 168°/0·01 mm. (Found: C, 72·1; H, 11·1; N, 17·0. $C_{15}H_{27}N_3$ requires C, 72·3; H, 10·8; N, 16·9%). Yield, 50 g.; 55%.

N-*δ-Diethylamino-α-methyl*-n-*butyl*-p-*phenylenediamine* (VI, R = CHMe·$[CH_2]_3$·NEt_2) was similarly prepared, except that the temperature during anil formation was not raised above 180°, since a higher temperature caused spontaneous decomposition. This *amine*, a colourless oil, had b. p. 174°/0·05 mm. (Found: C, 71·9; H, 10·7; N, 16·9%). Yield, 20 g.; 23%.

p-*Methoxyphenylcyanamide* (IV, R = OMe).—*p*-Methoxyphenylthiourea (30 g.), potassium hydroxide (43 g.), lead acetate (85 g.), and water (430 c.c.) were stirred during heating on a steam-bath for 15 minutes. The lead sulphide was then collected, and the filtrate acidified with 10% acetic acid and cooled. The crude product was filtered off, dissolved in 5% sodium hydroxide (150 c.c.), and cautiously reprecipitated by the addition of 5% acetic acid. Careful neutralisation resulted in the almost complete separation of a pale yellow amorphous material (*ca.* 1 g.) which was collected; acidification of the filtrate then caused the required product to separate in short needles. A second similar purification gave the *cyanamide* as colourless needles, m. p. 86—87° (Found: C, 64·8; H, 5·6. $C_8H_8ON_2$ requires C, 64·8; H, 5·4%): 10 g., 40%.

N-p-*Methoxyphenyl*-N′-m-*nitrophenylguanidine*.—*p*-Methoxyphenylcyanamide (7 g.) and *m*-nitroaniline hydrochloride (8·5 g., 1 mol.) were dissolved in alcohol (35 c.c.) and heated under reflux for 24 hours. The whole was then poured into 2% acetic acid (1 l.) and filtered. The filtrate was basified (sodium hydroxide) and the crude product collected. Two recrystallisations from 50% aqueous alcohol gave the pure *guanidine*, orange-red needles, m. p. 142° (Found: C, 58·3; H, 5·2; N, 19·6. $C_{14}H_{14}O_3N_4$ requires C, 58·7; H, 4·9; N, 19·6%): 8 g., 55%. The hydrochloride formed colourless needles, m. p. 128—136° (Found: C, 52·5; H, 4·6; N, 17·2. $C_{14}H_{14}O_3N_4$,HCl requires C, 52·1; H, 4·7; N, 17·4%).

N-p-*Methoxyphenyl*-N′-m-*aminophenylguanidine Hydrochloride* (II, R = OMe, R′ = H).—A solution of the above hydrochloride (8 g.) in alcohol (200 c.c.) was hydrogenated (Adams's catalyst, 0·2 g.) at room temperature and atmospheric pressure. The filtered solution was evaporated to *ca.* 50 c.c. and, on cooling, the *amino-guanidine hydrochloride* crystallised. Recrystallisation from alcohol gave small crystals, m. p. 212° (Found: C, 57·8; H, 6·0; N, 20·1. $C_{14}H_{16}ON_4$,HCl requires C, 57·4; H, 5·9; N, 20·05%). Yield, 5 g.; 70%.

N-p-*Methoxyphenyl*-N′-p-*β-diethylaminoethylaminophenylguanidine* (III, R = OMe, R′ = CH_2·CH_2·NEt_2).—*p*-Methoxyphenylcyanamide (7·5 g.) and *N-β*-diethylaminoethyl-*p*-phenylenediamine

(10·5 g.) were dissolved together in ethyl alcohol (35 c.c.) containing hydrogen chloride (2·9 g.) and refluxed for 36 hours. Evaporation followed by trituration of the residue with 5% aqueous ammonia gave a brown gum which was washed and dried. Repeated extraction with hot light petroleum (b. p. 40—60°) afforded, on cooling, a pale brown gum (1 g.). This was shaken with ether (20 c.c.), the ethereal solution evaporated, and the residue re-extracted with hot light petroleum. On cooling, the *guanidine* separated as a pale brown gum which was almost pure (Found: C, 68·3; H, 8·7; N, 19·1. $C_{20}H_{29}ON_5$ requires C, 67·6; H, 8·2; N, 19·7%). Yield, 0·7 g.; 4%. Neither the base nor any salts could be obtained crystalline.

This research was carried out on behalf of the Medical Research Council under a wartime collaborative agreement on antimalarial research between the Medical Research Council and Imperial Chemical Industries Ltd. We are greatly indebted to the Council for grants (F. T. N., J. W. G. P.) and to Imperial Chemical Industries Ltd., both for materials and for carrying out the antimalarial tests.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 30th*, 1946.]

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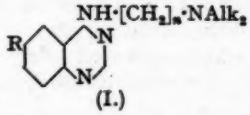
170. *Synthetic Antimalarials. Part XX. Cinnolines. Part XIII. Synthesis and Antimalarial Action of 4-Aminoalkylaminocinnolines.*

By J. R. KENEFORD and J. C. E. SIMPSON.

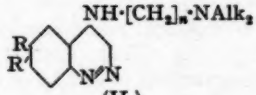
The preparation of a series of 6- and 7-substituted 4-aminoalkylaminocinnolines is described, and their antimalarial activities are recorded.

THE cinnoline ring-system is one which has obvious potentialities as a vehicle for the production of chemotherapeutic agents. As a result of earlier work (*J.*, 1942, 353; 1943, 447; 1945, 512, 520; 1946, 673; this vol., pp. 227, 232) having as its objective the consolidation of routes leading to different types of 4-substituted cinnolines, we were in a position to investigate the chemotherapeutic possibilities which this field appeared to offer, and we decided first to attempt to prepare compounds having antimalarial activity. Our interest in this problem was given additional stimulus by the fact that, when the work was begun, the bulk of the published synthetic work relating to the chemotherapy of malaria was restricted to derivatives of acridine and quinoline, although a few aminoalkylaminoquinazolines of type (I; R = Cl or NO_2) had been synthesised by Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, **8**, 1797; *Chem. Abs.*, 1939, **33**, 4993); these compounds, however, were stated to be devoid of antimalarial activity.

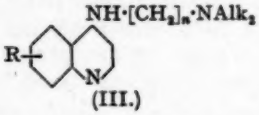
Preliminary results with cinnoline derivatives of type (II; R = H or OMe; R′ = H) (Simpson and Schofield, *Nature*, 1946, **157**, 439) suggested that activity might be expected in suitably substituted compounds, and in this paper we describe the preparation of a series of derivatives of type (II) substituted at C_6 and C_7. In choosing these positions of nuclear substitution we were guided partly by the accessibility of intermediates and partly by the fact that antimalarial activity is recorded for 4-aminoalkylaminoquinolines substituted in the same positions (III; R at C_6 or C_7) (Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1; B.P. Appl. 27673/38).



(I.)



(II.)

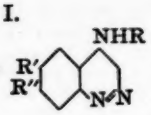


(III.)

The compounds listed in Table III were prepared by conversion of the requisite 4-hydroxycinnoline (*J.*, 1945, 520; this vol., pp. 227, 232) into the 4-chloro- and thence into the 4-phenoxy-derivative, followed by condensation of the latter with the appropriate amine; the use of phenoxy- instead of chloro-compounds for this reaction was more convenient, as most 4-chlorocinnolines decompose on storage, whereas the phenoxy-compounds can be kept indefinitely. The yield of 7-chloro-4-hydroxycinnoline was raised from 30% (this vol., p. 232) to 90% by the use of concentrated hydrochloric acid for the final stage, and we have found that this modification is of general applicability to the preparation in high yield of 4-hydroxycinnolines which do not contain an electron-attractive group in positions 6 or 8.

The compounds (I) were tested against *P. gallinaceum* in chicks at the Blackley laboratories of Imperial Chemical Industries Limited by the method of Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139), and the results [including, for purposes of comparison, those of Simpson and Schofield (*loc. cit.*)] are shown in Table I. Inspection of these results leads to the following conclusions: (*a*) Combination of the side-chain characteristic of mepacrine and

TABLE I.

Compounds of type 

Ref. No.	R.	R′.	R″.	Dose (mg./kg.).	Activity.*
3309	$CHMe\cdot[CH_2]_3\cdot NEt_2$	H	H	250	++
				120	+
6022	,,	H	Cl	80	++
				40	++
5655	,,	Cl	H	160	+ to ++
				80	—
5654	,,	Br	H	160	+ to ++
				80	—
4404	,,	OMe	H	80	—
5656	,,	Cl	Cl	160	++
				80	+ to ++
				40	
				20	—
5659	,,	Cl	Me	160	+ to ++
				80	+
3602	$[CH_2]_3\cdot NEt_2$	H	H	200	±
				120	—
6024	,,	H	Cl	80	+
5853	,,	Cl	Cl	80	—
6023	$[CH_2]_3\cdot NEt_2$	H	Cl	80	++
				40	+
5852	,,	Cl	Cl	80	+
6021	$[CH_2]_3\cdot NMe_2$	H	Cl	80	+ to ++
				40	+
5657	,,	Cl	Cl	160	+ to ++
				80	±
5658	,,	Cl	Me	160	+ to ++
				80	+
6025	$[CH_2]_3\cdot NBu^n_2$	H	Cl	80	+
5854	,,	Cl	Cl	80	—
6026	$[CH_2]_3\cdot N\cdot C_5N_{10}$	H	Cl	80	+
5855	,,	Cl	Cl	80	—

* Activity is shown as marked (++), slight (+), doubtful (±), or inactive (−).

pamaquin with a suitably substituted nucleus results in considerably greater activity than does the combination of other side-chains with the same nuclei (compare, *e.g.*, 3309, 6022, 5656 with 3602, 6024, 5853); (*b*) substitution at C_7, *ceteris paribus*, increases the antimalarial activity; (*c*) substitution at C_6 exerts a pronounced dystherapeutic effect. These conclusions are meant to apply only to the range of compounds studied; a discussion of their possible significance is held over pending the accumulation of further data.

The following compounds were tested for prophylactic activity against *P. gallinaceum* in chicks by the method of Davey (*Ann. Trop. Med. Parasit.*, 1946, **40**, 52) but found to be inactive; 5654, 5659, 6022, 6023, and 6024 at 80 mg./kg., and 6024, 6025, and 6026 at 160 mg./kg.

A paper by Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419), which appeared after completion of this work, describes the preparation of 6023 and of 6-bromo-4-γ-diethylaminopropyl-

TABLE II.

4-Phenoxycinnolines.

Substituent at					Analysis.					
					Found, %.			Required, %.		
6.	7.	M. p.	Formula.	Crystalline form.	C.	H.	N.	C.	H.	N.
H	H	94—95°	$C_{14}H_{10}ON_2$	Colourless needles or leaflets [1]	75·5	4·45	12·9	75·6	4·55	12·6
H	Cl	127—128	$C_{14}H_9ON_2Cl$	Colourless needles [2]	65·4	3·7	—	65·5	3·55	—
Cl	H	128—129	$C_{14}H_9ON_2Cl$	,, [2]	65·2	3·45	—	65·5	3·55	—
Br	H	151·5—152	$C_{14}H_9ON_2Br$	,, [2]	55·6	3·2	—	55·8	3·0	—
OMe	H	108—109	$C_{15}H_{12}O_2N_2$	,, [3]	71·0	4·45	—	71·4	4·8	—
Cl	Me	154—155	$C_{15}H_{11}ON_2Cl$	,, [2]	66·2	3·95	10·6	66·5	4·1	10·35

[1] From ether–ligroin (b. p. 40—60°). [2] From alcohol.
[3] From aqueous alcohol.

TABLE III.

4-Aminoalkylaminocinnolines.

Ref. No.	Substituent at 4.	6.	7.	M. p.	Formula.	Reaction conditions.	Crystalline form.	Analysis. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
5655	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	Cl	H	107—108°	$C_{17}H_{26}N_4Cl$	150°/2 hr.	Colourless micro-needles [1]	63·3	8·05	—	11·25	63·6	7·85	—	11·1
5654	,,	Br	H	97·5—98·5	$C_{17}H_{25}N_4Br$	,,	Colourless needles [1]	55·6	7·05	15·35	—	55·9	6·9	15·3	—
5656	,,	Cl	Cl	121·5—123	$C_{17}H_{24}N_4Cl_2$	130°/2½ hr.	Colourless micro-needles [1]	57·45	6·55	15·2	20·2	57·4	6·8	15·8	20·0
5659	,,	Cl	Me	120—121	$C_{18}H_{27}N_4Cl$	170°/2½ hr.	Colourless micro-needles [1]	64·75	8·25	16·7	—	64·55	8·1	16·7	—
6022	,,	H	Cl	123·5—124·5	$C_{17}H_{25}N_4Cl$	150°/2 hr.	Cream-coloured micro-needles [2]	63·65	7·8	17·2	—	63·6	7·9	17·5	—
5853	NH·[CH$_2$]$_2$·NEt$_2$	Cl	Cl	204—204·5	$C_{14}H_{18}N_4Cl_2$	130°/¼ hr.	Pale yellow glistening plates [3]	53·9	5·7	17·75	—	53·7	5·8	17·9	—
6024	,,	H	Cl	182·5—183·5	$C_{14}H_{19}N_4Cl$	,,	Cream-coloured hair-like needles [3]	60·4	6·65	19·7	—	60·3	6·9	20·1	—
5657	NH·[CH$_2$]$_2$·NMe$_2$	Cl	Cl	170—171	$C_{13}H_{16}N_4Cl_2$	,,	Small colourless blades [3]	52·45	5·4	18·75	23·85	52·2	5·4	18·7	23·7
5658	,,	Cl	Me	168—170	$C_{14}H_{19}N_4Cl$	,,	Colourless lustrous plates [4]	60·35	6·85	19·85	—	60·3	6·9	20·1	—
6021	,,	H	Cl	175—176	$C_{13}H_{17}N_4Cl$	,,	Long colourless needles [3]	59·1	6·65	20·75	—	58·95	6·5	21·2	—
5852	NH·[CH$_2$]$_3$·NEt$_2$	Cl	Cl	151·5—152·5	$C_{15}H_{20}N_4Cl_2$	,,	Dull micro-crystals [1]	55·35	6·15	17·1	—	55·0	6·2	17·1	—
6023	,,	H	Cl	162—163 [5]	$C_{15}H_{21}N_4Cl$	,,	Lustrous cream-coloured tablets [2]	61·45	7·4	18·9	—	61·5	7·2	19·1	—
5854	NH·[CH$_2$]$_3$·NBu$^n_2$	Cl	Cl	153·5—154	$C_{19}H_{28}N_4Cl_2$	,,	Colourless micro-needles [3]	59·5	7·25	—	18·35	59·5	7·4	—	18·5
6025	,,	H	Cl	123—124	$C_{19}H_{29}N_4Cl$	,,	Cream-coloured micro-needles [6]	65·3	8·3	15·7	—	65·4	8·4	16·1	—
5855	NH·[CH$_2$]$_3$·N·C$_5$H$_{10}$	Cl	Cl	214—215	$C_{16}H_{20}N_4Cl_2$	,,	Lustrous prismatic needles [3]	56·95	6·05	—	21·3	56·6	5·95	—	20·9
6026	,,	H	Cl	180—181	$C_{16}H_{21}N_4Cl$	,,	Lustrous narrow plates [3]	62·55	7·1	18·15	—	63·0	6·95	18·4	—

[1] From ether. [2] From ethyl acetate. [3] From alcohol. [4] From benzene.
[5] Leonard and Boyd (*loc. cit.*) give m. p. 164—165°. [6] From benzene–ligroin (b. p. 60—80°).

aminocinnoline; these compounds, for which no antimalarial results are yet recorded, were made directly from the chlorocinnolines and the amine.

Experimental.

M. ps. are uncorrected Derivatives of 4-hydroxy- and 4-hydroxy-6-methoxy-cinnoline were prepared by Dr. K. Schofield. All the reactions could apparently be carried out on any desired scale without loss of yield.

Improved Preparation of 7-Chloro-4-hydroxycinnoline.—Diazotisation was effected in hydrochloric acid, followed by heating on the steam-bath at 60° (cf. this vol., p. 232). It was found that the yield of cinnoline increased with an increase in concentration of acid up to *ca.* 8·5N; the yield was then 90—95%, and no significant increase resulted with higher concentrations. The ratio amino-ketone : acid medium varied between 1 : 60 and 1 : 100.

Similar results were obtained in the preparation of 4-hydroxycinnoline (70—75% yield in 9—9·5N-hydrochloric acid; contrast *J.*, 1945 520); amino-ketone : acid medium = *ca.* 1 : 100.

In each set of experiments the acid concentrations were calculated after addition of the nitrite solution, and the time of reaction was 4—5 hours. The products were isolated by evaporation under reduced pressure (this gave 4-hydroxycinnoline as hydrochloride, but in the case of the 7-chloro-compound much free base crystallised from the reaction mixture).

Preparation of 4-Chlorocinnolines.—The appropriate 4-hydroxycinnoline (1 mol.), phosphorus pentachloride (*ca.* 2 mols.), and phosphorus oxychloride (*ca.* 6 mols.) were heated on the steam-bath for 1 hour. The reaction was usually rapid; the hydroxycinnoline dissolved, and the chlorocinnoline crystallised from the hot solution. The mixture was poured on ice, made just alkaline with aqueous sodium hydroxide, and extracted with ether. The extract was washed with very dilute sodium hydroxide and water, dried, and concentrated (in the case of 4-hydroxycinnoline this was done under reduced pressure); yields of crude products were 80—90%. 4-Anilinocinnolines, by which the chlorocinnolines were occasionally characterised, were made by warming the reactants on the steam-bath for a few minutes, followed by crystallisation of the products from alcohol or ammoniacal alcohol.

4-Chlorocinnoline formed very pale yellow needles, m. p. 78—79°, from ether–ligroin (b. p. 40—60°); Busch and Klett (*Ber.*, 1892, **25**, 2847) and Leonard and Boyd (*loc. cit.*) give m. p. 79° and 76—77° respectively. The compound is unstable and decomposes very rapidly when warmed either alone or with acids. 4-Anilinocinnoline formed pale yellow silky needles, m. p. 229·5—230·5° (Busch and Klett, *loc. cit.*, give m.p. 232°) (Found : N, 19·0. Calc. for $C_{14}H_{11}N_3$: N, 19·0%). 4-Chloro-6-bromocinnoline, pale yellow needles, had m. p. 136—138° [Leonard and Boyd, *loc. cit.*, give 136—137° and 127—128° (interconvertible)]. 4 : 7-Dichlorocinnoline formed colourless polyhedra, m. p. 143—144° (Found : C, 48·3; H, 2·1; Cl, 35·4. Calc. for $C_8H_4N_2Cl_2$: C, 48·2; H, 2·0; Cl, 35·7%); Leonard and Boyd give m. p. 143—143·5°. The 4 : 6-isomer, soft pale yellow needles, had m. p. 111—112°, and 4 : 6-dichloro-7-methylcinnoline crystallised in small cream-coloured needles, m. p. 176—177°. *4-Chloro-6-methoxycinnoline* formed colourless hair-like needles, m. p. 149—151°, from ether (Found : Cl, 18·4. $C_9H_7ON_2Cl$ requires Cl, 18·25%), and yielded *4-anilino-6-methoxycinnoline* (pale yellow needles, m. p. 235·5—236°) (Found : C, 71·6; H, 5·25. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2%).

Preparation of 4-Phenoxycinnolines.—The chloro-compound (1 mol.) was added to a solution of powdered potassium hydroxide (1·2 mols.) in phenol (*ca.* 7·5 mols.), and the whole was heated on the steam-bath for 1 hour (the reaction with 4-chloro-6-methoxycinnoline was sluggish, and a reaction time of 6 hours was used). The mixture was poured into excess of aqueous sodium hydroxide and extracted with ether, after which the extract was repeatedly washed with sodium hydroxide solution and water, dried, and concentrated, giving the phenoxy-compounds (see Table II) in yields of 80—95%.

Preparation of 4-Aminoalkylaminocinnolines.—The phenoxy-compound (1 mol.) and aliphatic amine (*ca.* 2 mols.) were heated in an oil-bath, completion of the reaction being ascertained by examination of a sample of the material which (except in the reactions with δ-diethylamino-α-methylbutylamine) crystallised on cooling. The cold mixtures were filtered after addition of ether and the solid bases crystallised from the appropriate solvent (yields, 90—95%). The reactions in which δ-diethylamino-α-methylbutylamine was used were more sluggish than those with other amines, and the products from them were worked up by basification with aqueous sodium hydroxide and extraction with ether; the ethereal solutions were extracted with 33% aqueous acetic acid, the latter basified, and the products again taken into ether, which was washed, dried, and evaporated; excess of fatty amine was then removed at 90—110°/0·2—0·5 mm., and the residues recrystallised (yields were 65—75%). Distillation of the aminoalkylaminocinnolines was unsuccessful in the few cases tried owing to decomposition. **4404** was prepared by heating the chloro-compound and amine in phenol at 170°; **3602** was formed when 4-chlorocinnoline and the amine were heated at 130° without solvent under nitrogen, but was best prepared *via* the phenoxy-compound.

This investigation was carried out as part of a wartime programme of antimalarial research sponsored by the Medical Research Council in collaboration with Imperial Chemical Industries Limited. We are indebted to the former for a Research Studentship (J. R. K.) and to the latter for materials and for carrying out the biological tests. We are also greatly indebted to the workers of Imperial Chemical Industries for many discussions on the above work.

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171. *The Effect of Temperature on the Proportions of Isomers formed in the Mononitration of Toluene.*

By W. W. Jones and M. Russell.

Toluene has been nitrated with mixtures of nitric and sulphuric acids at various temperatures from − 30° to 60°. The proportion of *m*-nitrotoluene formed in each instance has been calculated from the setting point of the derived TNT. The results afford evidence that in applying the Arrhenius equation $k = nAe^{-E/RT}$ to the mononitration of toluene, $A_o = 2{\cdot}90\,A_m$, $A_p = 2{\cdot}70\,A_m$, $E_m - E_o = 917$ and $E_m - E_p = 1103$ cal. deg.$^{-1}$ mol.$^{-1}$.

The manufacture of trinitrotoluene is complicated by the undesirable formation of *m*-nitrotoluene in the mononitration stage. Several workers have published data on the proportions of isomers formed in the mononitration of toluene at various temperatures and in several media. Their results, for percentage *m*-nitrotoluene, are collected in Table I. Generally

Table I.

			C.				
Temp.	A.	B.	*a*.	*b*.	*c*.	D.	E.
−30°	2·7	3·5	—	—	—	—	—
0	3·1	3·9	2·5	4·5	3·3	3·7	—
20	—	—	4·3	4·5	3·9	—	4·1
30	3·2	4·4	—	—	—	4·4	—
40	—	—	—	4·2	—	—	—
50	—	—	—	4·3	—	—	—
60	4·0	5·1	—	—	—	—	—

A. Van den Arend, *Rec. Trav. chim.*, 1909, **28**, 408. Nitration in 85% HNO_3.
B. Holleman, Vermeulen, and de Mooy, *ibid.*, 1914, **33**, 1. Recalculation of results of Van den Arend.
C. Gibson, Duckham, and Fairbairn, *J.*, 1922, **121**, 270. Nitration in:
(*a*) 94% HNO_3;
(*b*) Mixed acid containing 58·7% H_2SO_4, 23·8% HNO_3, 17·5% H_2O;
(*c*) Mixed acid containing 64·4% H_2SO_4, 13·7% HNO_3, 21·9% H_2O.
D. Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959. Nitration in acetic anhydride and in nitromethane.
E. de Beule, *Bull. Soc. chim. Belg.*, 1933, **42**, 27. Nitration in HNO_3 and mixed acid.

the proportions of isomers were determined by thermal analysis, but Ingold *et al.* (*loc. cit.*) also determined the meta-content by solubility measurements on the derived nitrobenzoic acids.

The figures recorded in Table I show rather wide variations and, in particular, they indicate that change in meta-nitration with temperature is much less for nitration in mixed acid than in other media. Because of its technical importance, nitration in mixed acid has been reinvestigated, using a new method of analysis which is simpler and considered to be less liable to error than thermal analysis.

2 : 4-Dinitrotoluene, *p*-nitrotoluene, and known mixtures of *m*- and *p*-nitrotoluene were trinitrated by the standard method described in the experimental part, and the setting points of

Table II.

	2 : 4-DNT.	Mixtures of *m*- and *p*-nitrotoluene.				
Concn. of *m*-nitrotoluene (%) ...	—	0	2·11	3·22	4·58	5·75
Setting point of TNT, found	80·80°	80·78°	79·87°	79·26°	78·70°	78·13°
,, ,, ,, , calc.	—	80·80°	79·82°	79·30°	78·67°	78·13°

the products were determined. The results are recorded in Table II, the setting points being corrected. Setting points have been calculated from the equation:

$$\text{Setting point} = 80{\cdot}80 - 0{\cdot}465\ (\text{concn. of } m\text{-nitrotoluene}) \quad . \quad . \quad . \quad . \quad (1)$$

which was derived from the data by the method of least differences. That trinitration in these experiments was substantially complete is shown by the close agreement between the setting points of products derived from *p*-nitrotoluene and 2 : 4-dinitrotoluene with that recorded by Rintoul (*J. Soc. Chem. Ind.*, 1915, **34**, 60).

Toluene was nitrated at various temperatures with 1·2 mols. of nitric acid in the form of a mixed acid. The nitrotoluenes, after removal of unchanged toluene, were trinitrated by the

standard method. The setting points of the trinitrotoluenes were determined and the proportions of *m*-nitrotoluene in the original nitrotoluenes were calculated from equation (1). The results,

TABLE III.

Temperature of mononitration	−30°	0°	30°	60°
Setting point of TNT	79·42°	79·09°	78·76°	78·52°
Concn. of *m*-nitrotoluene (%)	2·97	3·68	4·39	4·90

collected in Table III, show that the proportion of *m*-nitrotoluene changes almost linearly with temperature and there is no evidence that the rate of change is less for mixed acid nitrations than for nitrations in other media.

DISCUSSION.

Bradfield and Jones (*J.*, 1928, 1006) calculated, for several substitutions, the proportions of isomers formed at one temperature from the experimentally determined proportions at a second temperature by means of the Arrhenius equation, $k = nAe^{-E/RT}$, in which, for each isomer, k is the rate of formation, n is the number of equivalent substitution positions, A is a temperature-independent factor, E is the energy of activation, and T is the absolute temperature. They obtained fair agreement with experiment on the assumption that A was the same for each isomer formed in a particular reaction. The close agreement, for the proportion of *m*-nitrotoluene formed at 0° and 30°, between our results and those of Ingold *et al.*, determined by entirely different techniques, is strong evidence for the essential reliability of the experimental data. The values for *m*-nitrotoluene, calculated for other temperatures by the method of Bradfield and Jones from the data of Ingold *et al.* at 30°, are given in the left side of Table IV. They show increasing divergence from our experimental values as the temperatures depart from 30°. As these deviations are considerable and show a systematic trend they cannot be attributed to experimental error.

Better agreement between calculated and experimental results can be obtained only by assuming that the temperature-independent factors are different for the three isomers. Appropriate values for these factors can be calculated from the proportions of isomers at two temperatures, thus:

$$\text{Let } k_o = 2A_o e^{-E_o/RT};\ k_m = 2A_m e^{-E_m/RT};\ k_p = A_p e^{-E_p/RT}$$

$$\text{Then } k_o/k_m = (A_o/A_m)e^{(E_m - E_o)/RT}$$

If r_1 and r_2 are the ratios of *o*- to *m*-nitrotoluene formed at two temperatures T_1 and T_2, then

$$2{\cdot}303\{\log_{10} r_1 - \log_{10}(A_o/A_m)\} = (E_m - E_o)/RT_1 \quad . \quad . \quad . \quad . \quad (2)$$

$$\text{and } 2{\cdot}303\{\log_{10} r_2 - \log_{10}(A_o/A_m)\} = (E_m - E_o)/RT_2$$

Dividing and transposing we obtain

$$\log_{10}(A_o/A_m) = (T_2 \log_{10} r_2 - T_1 \log_{10} r_1)/(T_2 - T_1). \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Similarly, if s_1 and s_2 are the ratios of *p*- to *m*-nitrotoluene at T_1 and T_2,

$$\log_{10}(A_p/2A_m) = (T_2 \log_{10} s_2 - T_1 \log_{10} s_1)/(T_2 - T_1) \quad . \quad . \quad . \quad . \quad . \quad (4)$$

By substituting in equations (3) and (4) the ratios of isomers given by Ingold *et al.* for 0° and 30° it was found that

$$A_o = 2{\cdot}90A_m \text{ and } A_p = 2{\cdot}70A_m,$$

and by further calculation the proportions of isomers formed at − 30° and 60°, shown in the right side of Table IV, were obtained. It is evident that much better agreement with experiment is given by the new equations.

TABLE IV.

	$A_o = A_m = A_p$.			$A_o = 2{\cdot}90A_m$; $A_p = 2{\cdot}70A_m$.		
Temp.	*o* (%).	*m* (%).	*p* (%).	*o* (%).	*m* (%).	*p* (%).
−30°	58·33	2·32	39·35	57·55	2·98	39·47
0	58·49	3·31	38·20	(58·10)	(3·70)	(38·20)
30	(58·45)	(4·40)	(37·15)	(58·45)	(4·40)	(37·15)
60	58·21	5·54	36·25	58·66	5·07	36·27

The numbers in parentheses are the experimental values on which the calculations are based.

The values of A_o and A_p are nearly equal and only small changes in the proportions of *o*- and *p*-nitrotoluene, but none in the proportions of *m*-nitrotoluene, are caused by adopting the mean value, 2·80, for both. There does not, however, appear to be any reason why, in the general case, A_o should be equal to A_p and so the separate values have been used in the calculations of Table IV.

From equation (2) and the corresponding equation for the ratio of *p*- to *m*-nitrotoluene we have obtained the following values, in cal. deg.$^{-1}$ mol.$^{-1}$, for activation energy differences :

$$E_m - E_o = 917 \qquad E_m - E_p = 1103$$

Experimental.

Materials.—" Nitration " toluene (National Benzole Specification No. 7, 1938) was distilled through a short column. The middle fraction, having $d_{15.6°}^{15.6°}$ 0·8710, $n^{20°}$ 1·4963, was used. Commercial *m*-nitrotoluene was purified by fractional freezing until the maximum setting point, 16·0° (corr.), was reached. Commercial *p*-nitrotoluene and 2 : 4-dinitrotoluene were recrystallised from alcohol until the setting points remained unchanged at 51·6° (corr.) and 69·8° (corr.).

A stock of mononitration mixed acid was made from sulphuric acid (*d* 1·84, 18·8 kg.), nitric acid (*d* 1·42, 1·1 kg.), liquid nitrogen tetroxide (0·9 kg.), and water (4·7 kg.). Analysis of the mixture gave 71·4% H_2SO_4, 5·35% HNO_3, 1·75% HNO_2, and 21·5% H_2O. Nitrous acid was added because it catalyses the nitration and prevents undue temperature fluctuations in the early stages. Dinitration and trinitration acids were made up as required for each nitation from concentrated sulphuric and nitric acids and 20% oleum that had been titrated.

Mononitration.—The all-glass apparatus was a 2-l., 3-necked, bolt-head flask fitted with paddle stirrer, reflux condenser, dropping funnel, and thermometer, the last two reaching to near the bottom. The flask was immersed in a suitable cooling bath : solid carbon dioxide and trichloroethylene for — 30° and 0°, ice-water for 30°, and water at the ordinary temperature for 60°. Mixed acid (2300 g.) was placed in the nitrator and cooled to just below the reaction temperature, and toluene (150 g.) was run in, fairly rapidly at first till the intended temperature was reached and then more slowly to keep the temperature constant. After the initial warming up, the maximum variation in temperature was $\pm$ 1°. The addition of toluene took about 30 minutes, and the reaction was continued for a further 75 minutes except for the — 30° nitration which was run for a total time of 4·5 hours. During the later stages of the reaction the bath temperature was raised gradually to keep the reaction temperature constant until, finally, outside and inside temperatures were almost equal. The reaction mixture was poured into ice-water (4 kg.), the aqueous layer was removed, and more water was added followed by ether until the organic layer was the lighter. The ethereal layer was washed with water till acid-free and dried (Na_2SO_4), and the ether was distilled off. Traces of ether and any un-nitrated toluene were removed by passing a current of air through the residue heated to 100° under reduced pressure. The nitrotoluenes were tested colorimetrically for toluene by shaking with an equal volume of a solution of sodium nitrite (2·5 g.) in 88% sulphuric acid (100 c.c.). Absence of a red colour indicates less than 0·2% of toluene (Dr. J. K. N. Jones, private communication).

Dinitration.—The apparatus was similar to that used for mononitration, except that the flask was of 1 l. capacity. It was immersed in a stirred oil-bath provided with means for heating and cooling. Mononitrotoluene (50 g.) was dissolved in 90% sulphuric acid (120 g.) in the nitrator at 50°. Mixed acid (125 g.), containing 70·0% of sulphuric acid, 21·5% of nitric acid, and 8·5% of water, was added cautiously from the dropping funnel. As soon as reaction had started the bath was cooled to about 30° and the rate of addition controlled so that all the mixed acid was added at about 50° in 30 minutes. The mixture was then rapidly heated to 70° and this temperature maintained for 1·5 hours. The product was washed thrice at 100°, each time by stirring vigorously for 15 minutes with an equal volume of water, allowing to settle for 5 minutes, and separating the aqueous layer. Solid which separated from the washings on cooling was collected and added to the main product, and the whole was dried at 100° for 3 hours.

Trinitration.—The same apparatus was used as for dinitration. The whole of the dinitration product (or 65 g. in the case of 2 : 4-dinitrotoluene) was dissolved in 100% sulphuric acid (220 g.) in the nitrator at 100°, the oil-bath was cooled to about 97°, and the addition of mixed acid (125 g.), containing 60% of sulphuric acid, 40% of nitric acid, and 0% of water, was started. Reaction did not begin immediately, and the addition of mixed acid was stopped after a few g. had been added until there was a noticeable rise in temperature. The bath was then cooled to about 80° and the rate of addition controlled to keep the temperature at 100°. The addition was complete in 30 to 45 minutes. Towards the end of the addition of mixed acid the bath temperature was gradually raised so that it was 95° at the end of the addition, and it was further raised to about 98° during the additional reaction time of 3·5 hours. Finally, the reaction mixture was poured on ice and kept overnight, and the solid was then collected. The trinitrotoluene was washed with water at 100°, in the same manner as the dinitrotoluene, till the acidity of the last wash, titrated to phenolphthalien, was equivalent to not more than 0·002 g. of sulphuric acid. The washed trinitrotoluene was dried for 6 hours at 100° and its setting point determined. The observed value was corrected for exposed stem.

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172. *The Reaction of* 1-*Nitropropane with Formaldehyde and Ammonia.*

By E. L. Hirst, J. K. N. Jones, (Mrs.) S. Minahan, F. W. Ochynski, A. T. Thomas, and T. Urbanski.

Products of both high and low molecular weight are formed by the interaction of 1-nitropropane, formaldehyde, and ammonia. The reaction is shown to be essentially one of the type described by Mannich, in which the nitropropane provides the necessary active hydrogen atom. Amongst the products are ring compounds of the 1 : 3-tetrahydro-oxazine and 1-oxa-3-aza*cyclo*octane type.

Considerable interest has been shown recently in the chemistry of the nitro-paraffins (see, for example, Johnson and Degenry, *J. Amer. Chem. Soc.*, **1939**, **61**, 3194; Spring and Degenry, *ibid.*, **1942**, **64**, 1063; Senkus, *ibid.*, **1946**, **68**, 11; Johnson, *ibid.*, pp. 12, 14) and it is opportune to summarise work carried out during the past few years, but hitherto withheld from publication by reason of war-time secrecy regulations. One of the authors has previously shown that the large-scale preparation of nitro-paraffins was practicable (Urbanski, *Rocz. Chem.*, **1936**, **16**, 466; **1937**, **17**, 161; *Compt. rend.*, **1936**, **203**, 620; **1937**, **204**, 870) and has indicated their use for the production of combustible resins (Urbanski, B.P. Appln. 7681, 5th June, 1942; U.S.P. Appln. 488,456, 25th May, 1943). These resinous materials were made by the interaction of nitropropane, formaldehyde, and ammonia, and it was therefore of interest to investigate the nature of the reactions responsible for their formation. The present paper records some of the results obtained in a study of reactions which had not at that time been reported in the literature, despite the interest displayed by earlier workers (*e.g.*, Henry; Mousset; Duden, Bock, and Reid; Cerf de Mauny; Zief and Mason) in the condensation of formaldehyde, nitro-paraffins, and amines. The resins obtained from 1-nitropropane, formaldehyde, and ammonia are basic. The precise nature of the portion of high molecular weight is still uncertain, but the types of linkage are indicated by the structures of the accompanying materials of low molecular weight and by the nature of the decomposition products of the resinous materials.

The first stage in the series of reactions is the formation of 2-nitrobutanol (I) and 2-nitro-2-ethylpropane-1 : 3-diol (II). Since ammonia is present, together with formaldehyde, hexamethylenetetramine is also produced and this yields with (II) a molecular *complex*. When warmed in water this complex gives a resin similar to those obtained by the interaction of the three components. The mechanism of the reaction appears to resemble that of the Mannich reaction. From (II) and ammonia a *base* (III) is produced, and this then reacts with formaldehyde, giving the *N*-hydroxymethyl derivative (IV), which on cyclisation gives the *oxazine* (V). No evidence for the formation of *N*-methyl derivatives was obtained. Since only one of the hydrogen atoms in (V) can react with formaldehyde it follows that (V) cannot yield a polymer on further condensation, and its production in reactions designed to lead to resin formation is to be avoided. Under appropriate conditions, however, there may be as much as 30% of (V) present in the crude resin. It is an oil which can be separated by distillation or by precipitation of the crystalline *hydrochloride*, and yields with methyl iodide a crystalline *methiodide* (VI). The corresponding hydroxide decomposes when heated yielding nitrobutene and other decomposition products.

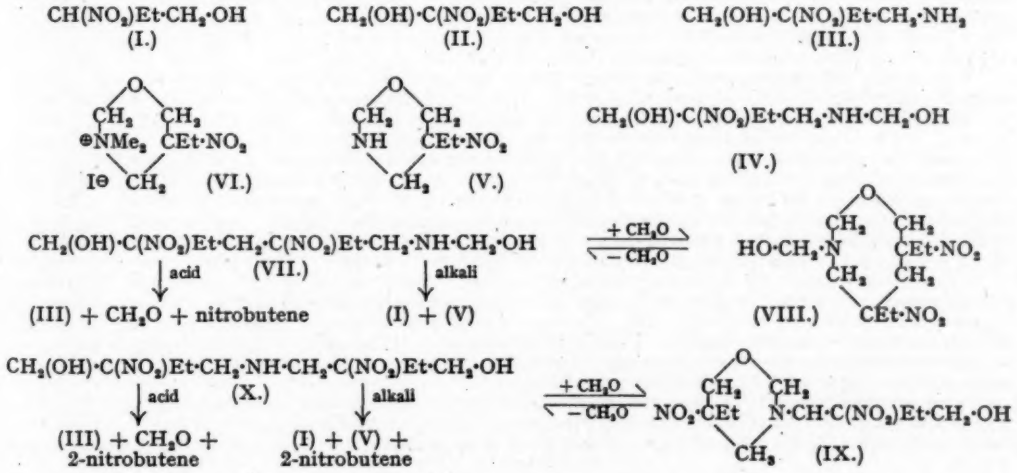
If the reaction between nitropropane, formaldehyde, and ammonia was interrupted shortly after the nitropropane had dissolved, an oily product was precipitated on cooling. It crystallised slowly, and either (VIII) or (X) was formed according to the conditions of the reaction, (VIII) being found when 1 mol. of ammonia was used per mol. of nitropropane, and (X) when 0·5 mol. of ammonia was used. (VIII) lost formaldehyde on being warmed with concentrated hydrochloric acid and gave the crystalline *hydrochloride* of (VII), and when the latter was warmed with formaldehyde it passed back into (VIII). The hydrochloride of (VII) gave a *picrate*; with sodium nitrite it gave an oily nitroso-compound which was reconverted into (VII) on being heated with concentrated hydrochloric acid, the presence of an imino-group being thus proved. The hydrochloride of (VII) when boiled in aqueous solution decomposed with the formation of the *hydrochloride* of (III), 2-nitrobutene, and formaldehyde. With aqueous sodium hydrogen carbonate it gave the crystalline base (VII) which decomposed on distillation in a vacuum giving (V) and (I). The formation of (VII) and (VIII) can be represented as an example of the Mannich reaction, and the formulæ suggested for these substances serve to explain their mode of origin and their chemical properties.

The *base* (IX) gives a series of reactions similar to those of (VIII). It dissolves in cold

concentrated hydrochloric acid giving a ***hydrochloride*** which hydrolyses in water, regenerating (IX). If (IX) is heated with dilute hydrochloric acid, 1 mol. of formaldehyde is eliminated and the ***hydrochloride*** of the secondary ***base*** (X) is formed. The hydrochloride of (X) when heated with aqueous formaldehyde regenerates the tertiary base (IX). The hydrochloride of (X) gave a well-defined ***picrate*** and an oily nitroso-compound which regenerated the hydrochloride of (X) when heated with concentrated hydrochloric acid, indicating the presence of an imino-group. The hydrochloride of (X) on treatment with aqueous sodium carbonate gave the corresponding crystalline base which decomposed when boiled with water or on distillation under reduced pressure with formation of (I), 2-nitrobutene, and (V). The hydrochloride of (X), on prolonged boiling with water, gave ammonium chloride, formaldehyde, 2-nitrobutene, and the hydrochloride of (III). The formation of (IX) and (X) and their chemical properties can most easily be explained by the mechanism shown in the accompanying scheme.

Substance (V) can be obtained from the resin by distillation under reduced pressure or by the action of hydrochloric acid, as well as by the decomposition of the bases (VII) and (X). It forms a picrate and hydrochloride and an oily nitroso-derivative. The hydrochloride when boiled with water eliminates 1 mol. of formaldehyde with formation of the hydrochloride of (III). This reaction is reversible, the hydrochloride of (III) regenerating the hydrochloride of (V) on crystallisation from propyl alcohol containing formaldehyde.

The base (III), which was unstable even at room temperature, is a primary amine, since it gives nitrogen with aqueous sodium nitrite. The action is, however, complex since the initial gentle evolution of nitrogen was followed by a violent reaction in which nitrous oxide, as well as nitrogen, was evolved and a greenish water-insoluble oil was produced.



Experimental.

Additive Compound $[(C_5H_{11}O_4N)_2,C_6H_{12}N_4]$ *of 2-Nitro-2-ethylpropane-1 : 3-diol and Hexamethylenetetramine.*—1-Nitropropane (1 mol., 89 g.) was added to a cold mixture of 40% formaldehyde (3 mols., 225 c.c.) and 33% ammonia (1 mol., 59 c.c.). The mixture was stirred at room temperature until the nitropropane disappeared (12—15 hours). After some time the aqueous solution was separated from an oily precipitate (containing 2-nitrobutanol). The addition of sodium chloride to the aqueous solution salted out an oil, which solidified in fine needles (100 g.). It was the additive compound of 2-nitro-2-ethylpropane-1 : 3-diol (3 mols.) and hexamethylenetetramine (1 mol.); white needles from chloroform, m. p. 117°. The additive *compound* is very readily soluble in water, soluble in alcohol, very slightly soluble in ether. It gave hexamethylenetetramine picrate, m. p. 179°, with picric acid, and hexamethylenetetramine hydrochloride with hydrochloric acid. It was dissociated in solution. For example, ebulliometric determination in chloroform gave *M*, 158 [calc. for hexamethylenetetramine, 140; for 2-nitro-2-ethylpropane-1 : 3-diol, 149. $(C_5H_{11}O_4N)_2,C_6H_{12}N_4$ requires *M*, 587]. When heated it was converted into a resin.

Another method for the preparation of the additive compound consisted in mixing concentrated aqueous solutions of 2-nitro-2-ethylpropane-1 : 3-diol (4·47 g.) with hexamethylenetetramine (1·40 g.). The crystalline additive product (4·2 g.) was precipitated on standing [Found : CH_2O, determined by the 2 : 4-dinitrophenylformhydrazone method, 30·5. $(C_5H_{11}O_4N)_2,C_6H_{12}N_4$ requires CH_2O, 30·8%].

Resin A.—1-Nitropropane (1 mol., 89 g.) was heated with 40% formaldehyde (3 mols., 225 c.c.) and 33% ammonia (1 mol., 59 c.c.) with stirring at 90—95° for 15—30 minutes. The reaction was then stopped by rapid cooling (pouring on ice). An oily layer containing nitro-olefins was separated

by decantation. The liquor was reheated and the temperature maintained at 90—95° for 8 hours with efficient stirring.

The resin formed a separate phase which was isolated by decantation. It was washed with hot water and dried in a partial vacuum. By evaporation of the liquor an additional quantity was obtained (yield, 110—125 g.).

Resin B.—2-Nitro-2-ethylpropane-1 : 3-diol (1 mol., 149 g.) was mixed with 40% formaldehyde (1 mol., 75 c.c.) and 33% ammonia (½ mol., 295 c.c.). The temperature was kept between 90° and 95° for 10 hours with stirring. The oily product was precipitated and, after cooling, was separated from the liquor, washed, and dried in partial vacuum (yield, 110 g.). The resin was a colourless and odourless viscid liquid.

Isolation of (V) *from resins* A *and* B. Fractionation of the resin under reduced pressure gave two fractions: (*a*) b. p. 140° (bath temp.)/0·01 mm., $n_D^{16°}$ 1·4720; (*b*) b. p. 160—180° (bath temp.)/0·01 mm., $n_D^{16°}$ 1·4880. Both fractions with methyl iodide gave a derivative, m. p. 218° (decomp.), identical with the methiodide of 5-nitro-3-methyl-5-ethyltetrahydro-1 : 3-oxazine (VI) described below. The liquid air trap of the distillation apparatus contained 2-nitrobutene and a blue nitroso-derivative of unknown constitution.

Isolation of (IX) *by steam distillation of the resin* A *or* B. The resin *A* or *B* (9·3 g.) was distilled in steam giving an oil (6 g.) which was mainly the base (V), since with methyl iodide it gave the crystalline methiodide (VI). The aqueous distillate was extracted with ether and then with benzene, and the combined extracts were dried (Na_2SO_4) and evaporated to a syrup (4 g.) under reduced pressure. The syrup crystallised on standing and, after tiling and recrystallising from benzene, *5-nitro-5-ethyl-3-(2-nitro-2-hydroxymethylbutyl)tetrahydro-1 : 3-oxazine* (IX), m. p. 101°, was isolated (Found: C, 45·4; H, 7·2; N, 13·9. $C_{11}H_{21}O_6N_3$ requires C, 45·4; H, 7·2; N, 14·4%).

Preparation of the Bases (VIII) *and* (IX).—1-Nitropropane (1 mol., 89 g.) was mixed with 40% formaldehyde (3 mols., 225 c.c.) and 33% ammonia (1 mol., 59 c.c.) and heated with stirring during 1½ hours at 90—95°. The hot solution was then poured into ice–water. The oily precipitate crystallised on standing (after *ca.* 2 weeks), yielding crystals of *5 : 7-dinitro-3-hydroxymethyl-5 : 7-diethyl-1-oxa-3-azacyclooctane* (VIII). Recrystallised from ether and then from chloroform or from benzene–light petroleum, it gave white needles, m. p. 97° (yield, 15—20 g.). It was soluble in hot water, cold ether, alcohol, acetone, and benzene, insoluble in light petroleum. It was less soluble in chloroform than (IX). Mixed with (IX) it gave considerable depression of m. p. (70—73°) [Found: C, 45·3; H, 7·0; *M* (ebulliometrically in benzene), 280. $C_{11}H_{21}O_6N_3$ requires C, 45·4; H, 7·2%; *M*, 291].

The base (VIII) gave with cold concentrated hydrochloric acid the *hydrochloride*, m. p. 174° (Found: C, 40·1; H, 6·7; N, 12·1; Cl, 10·9. $C_{11}H_{21}O_6N_3$,HCl requires C, 40·3; H, 6·5; N, 12·8; Cl, 10·8%). This hydrochloride hydrolysed in cold water yielding the free base (VIII). On being warmed with concentrated hydrochloric acid the hydrochloride lost one molecule of formaldehyde and was converted into the *hydrochloride* of hydroxymethyl-2 : 4-dinitro-4-hydroxymethyl-2-ethylhexylamine (VII), m. p. 179° (Found: CH_2O, 10·9. Loss of 1 mol. of CH_2O requires 10·3%). It depressed the m. p. of the hydrochloride of (VIII). This hydrochloride of (VII) was insoluble in ether, benzene, and chloroform, readily soluble in water and hot alcohol, sparingly soluble in cold alcohol. It recrystallised from alcohol in the form of small plates, m. p. 179° (decomp.) (Found: C, 38·4; H, 7·1; N, 12·4; Cl, 11·2. $C_{10}H_{21}O_6N_3$,HCl requires C, 38·0; H, 6·7; N, 13·3; Cl, 11·3%). On being heated with concentrated aqueous formaldehyde it gave an oil, which was extracted with ether; the dried extracts were evaporated in partial vacuum to a syrup, which crystallised slowly. After standing the crystals were triturated with ether and filtered. Recrystallisation from benzene gave the pure base (VIII), m. p. and mixed m. p. 97°. The hydrochloride of (VII) reacted with sodium nitrite and gave an oily nitroso-derivative soluble in ether. The latter regenerated the hydrochloride of (VII) on treatment with concentrated alcoholic hydrogen chloride.

The hydrochloride of (VII) was dissolved in alcohol and aqueous picric acid was added. The pale yellow *picrate* of (VII) was precipitated, m. p. 154° (Found: C, 38·2; H, 4·8; N, 16·4. $C_{16}H_{24}O_{13}N_6$ requires C, 37·8; H, 4·7; N, 16·5%). The picrate was unstable and could not be recrystallised from water.

The hydrochloride of (VII) (1·45 g.) was dissolved in water, and sodium hydrogen carbonate and ether were added. The syrupy base (1·33 g.) was isolated on evaporation of the solvent. The base (VII) (1·33 g.) on distillation under reduced pressure gave a fraction (0·74 g.), $n_D^{15°}$ 1·4670, b. p. 140° (bath temp.)/0·01 mm., and a still residue (0·35 g.). The volatile fraction consisted of the base (V) and 2-nitrobutanol. These were separated by dissolving the base in the calculated quantity of hydrochloric acid. The 2-nitrobutanol (I) was then extracted with ether. The base (V) was characterised by its hydrochloride, m. p. 203° (decomp.), and picrate, m. p. 153°, not depressed on admixture with an authentic specimen.

The hydrochloride of (VII) (888 mg.) was dissolved in water and the solution boiled. Decomposition occurred and formaldehyde and 2-nitrobutene distilled. The aqueous solution remaining in the flask was evaporated to dryness under reduced pressure and the residue (516 mg.) was triturated with acetone and filtered. The residue (68 mg.) was ammonium chloride. The acetone solution was evaporated to a syrup and triturated with ether; the hydrochloride of the base (III), m. p. 126° (see below), then crystallised. The aqueous distillate contained formaldehyde (Found: 9%; 1 mol. requires 9·5%) and 2-nitrobutene (characteristic odour, absorption of bromine, polymerises with alkali).

Preparation of (IX).—2-Nitro-2-ethylpropane-1 : 3-diol (1 mol., 149 g.) was heated with 40% formaldehyde (1 mol., 75 c.c.) and 33% ammonia (½ mol., 26 c.c.) at 95—96° for *ca.* 1½ hours. The product (IX) was isolated by pouring into ice–water. It recrystallised from ether, chloroform, or benzene–light petroleum in long needles, m. p. 101°. Yield, 50 g. [Found: C, 45·6; H, 7·0; N, 14·5; *M* (ebulliometrically in benzene), 285. Calc. for $C_{11}H_{21}O_6N_3$: C, 45·4; H, 7·2; N, 14·4%; *M*, 291].

A simple method of isolating the base (IX) from the resin *B* consisted in dissolving the resin in cold hydrochloric acid. The solution was poured on ice. The resinous substance precipitated was extracted

with ether, the extracts were dried and the ether was evaporated. The residue solidified into crystals of (IX), m. p. and mixed m. p. 98°.

The base (IX) reacted with cold concentrated hydrochloric acid, yielding the *hydrochloride*, m. p. 156° (Found: C, 40·4; H, 6·8; N, 12·6; Cl, 10·6. $C_{11}H_{21}O_6N_3$,HCl requires C, 40·3; H, 6·5; N, 12·8; Cl, 10·8%). The same product was obtained by passing hydrogen chloride through a solution of the base (IX) in chloroform or carbon tetrachloride. It is insoluble in ether or chloroform, soluble in alcohol. On dissolving in water it hydrolyses giving the free base (IX), m. p. 101° (Found: C, 45·1; H, 7·3; N, 13·3%).

Hydrochloride of (X).—The base (IX) or its hydrochloride, when heated with concentrated hydrochloric acid, lost a molecule of formaldehyde and was converted into the hydrochloride of bis-2-nitro-2-hydroxymethylbutylamine (X) (Found: CH_2O, 10·3. Loss of one mol. of CH_2O requires 10·3%). The *hydrochloride* separated in plates or needles from absolute alcohol, m. p. 186° (Found: C, 38·0; H, 6·8; N, 12·7; Cl, 11·2. $C_{10}H_{21}O_6N_3$,HCl requires C, 38·0; H, 6·7; N, 13·3; Cl, 11·3%). On warming an aqueous solution of the hydrochloride with formaldehyde solution (40%) an oil separated and was extracted with ether. The extract was dried (Na_2SO_4) and the ether removed; the base (IX) then crystallised. M. p. and mixed m. p. [with base (IX)] 99°.

The hydrochloride reacted with sodium nitrite solution giving the nitroso-derivative which separated as an oil. It was extracted with ether and the dried extracts were evaporated under reduced pressure. Concentrated hydrochloric acid reconverted it into the parent hydrochloride of (X), m. p. and mixed m. p. 186°.

Isolation of the Base (X).—The hydrochloride of (X) was dissolved in a minimum amount of water, and ether and excess of sodium hydrogen carbonate solution were added. The ethereal layer was separated and the aqueous solution extracted twice with ether. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to a syrup, which crystallised on trituration with a little ether. The *compound* separated in a good yield as a white crystalline solid, and was recrystallised from ether–light petroleum, m. p. 54° [Found: C, 43·1; H, 7·5; (OH), 11·8. $C_{10}H_{19}O_4N_3(OH)_2$ requires C, 42·9; H, 7·5; (OH), 11·3%]. The *picrate*, after recrystallisation from water, had m. p. 148° (Found: C, 37·8; H, 5·1; N, 16·7. $C_{16}H_{24}O_{13}N_6$ requires C, 37·8; H, 4·7; N, 16·5%).

On boiling an aqueous solution of the base (X) two molecules of formaldehyde were liberated (Found: CH_2O, 19%. Two mols. of CH_2O require 21·5%). On distillation under reduced pressure, the base (X) (1·4 g.) gave a fraction (0·9 g.), b. p. 140° (bath temp.)/0·01 mm., $n_D^{29°}$ 1·4665, containing basic material, and a still residue (unchanged material). With alcoholic hydrogen chloride the distillate gave the crystalline hydrochloride (V), m. p. 202°. Titration with dilute hydrochloric acid showed that some of the distillate was neutral and not soluble in acid. After neutralisation the solution was therefore extracted with ether and the extracts were distilled under reduced pressure giving a fraction (0·3 g.), b. p. 120° (bath temp.)/0·01 mm., $n_D^{15°}$ 1·4438. This was 2-nitrobutanol, $n_D^{15°}$ 1·4430.

The hydrochloride of (X) (385 mg.) was dissolved in water and heated at 93° for 12 hours. The solution was then evaporated under reduced pressure and the residue (202 mg.) was triturated with acetone. The insoluble material (18 mg.) was identified as ammonium chloride. The acetone solution on evaporation gave a crystalline solid, m. p. 126°. This was the hydrochloride of (III). The aqueous distillate was extracted with ether and the formaldehyde estimated in the aqueous solution (Found: CH_2O, 7. One mol. requires 9·3%). The ethereal extract on evaporation left an oil (10 mg.) which had the reactions of 2-nitrobutene. On heating the hydrochloride of (X) with sodium hydroxide solution and then adding acid and distilling, two molecules of formaldehyde were eliminated (Found: CH_2O, 18·0. 2 mols. of CH_2O require 19·0%).

Action of Concentrated Hydrochloric Acid on Resin A.—(*a*) The resin dissolved in concentrated hydrochloric acid with evolution of heat. The solution was then evaporated under reduced pressure to a syrup. On standing, crystals separated. They were fractionated into hydrochlorides of (V), (VII), (X), and (IV) by the differences of their solubilities in alcohol and ether. The hydrochloride of (V) is less soluble than that of (X), which in turn is less soluble than that of (VII). The most soluble is the hydrochloride of (IV). The yields varied, (IV) being obtained in the greatest proportion (up to 30% by weight of the resin). (VII) was not obtained from Resin *B*.

(*b*) The resin was dissolved in chloroform (or alcohol) and hydrogen chloride bubbled through the solution. The gas was strongly absorbed, the colour of the solution changed from light yellow to deep orange, heat was evolved, and an evolution of formaldehyde occurred. At first a thick emulsion appeared, which then crystallised. The crystals were separated and washed with chloroform and ether. Hydrogen chloride was again passed through the filtrate and a second crop of crystals was formed and separated. This was repeated several times and finally several fractions were collected, representing the hydrochlorides of the four bases mentioned above. Yield, 80 g. from 100 g. of Resin *A*.

The *hydrochloride* of 5-nitro-5-ethyltetrahydro-1 : 3-oxazine (V) was isolated in the form of white crystals, insoluble in ether, benzene, and chloroform, readily soluble in water and alcohol, m. p. 203° (decomp.) (Found: C, 36·8; H, 6·5; N, 13·9; Cl, 17·9. $C_6H_{12}O_3N_2$,HCl requires C, 36·7; H, 6·6; N, 14·2; Cl, 18·1%). Sodium nitrite converted it into an oily, pale yellow nitroso-derivative, soluble in hot water, insoluble in cold water, and volatile with steam. It was not decomposed on boiling with water. It distilled under reduced pressure, b. p. 130° (bath temp.)/0·01 mm., $n_D^{15°}$ 1·5000. The free *base* (V) was prepared from the hydrochloride (2·15 g.) by the action of sodium hydrogen carbonate and extraction with ether. Yield, 1·8 g. It is an oily liquid insoluble in water, $n_D^{15°}$ 1·4873 [Found: C, 45·4; H, 7·5; *M* (Rast), 162. $C_6H_{12}O_3N_2$ requires C, 45·1; H, 7·5%; *M*, 160]. The hydrochloride with aqueous picric acid gave a pale yellow *picrate*, m. p. 156° (Found: C, 36·8; H, 4·0; N, 18·0. $C_{12}H_{16}O_{10}N_8$ requires C, 37·0; H, 3·8; N, 18·0%).

Preparation of (VI).—The base (V) (2 g.) by the action of methyl iodide gave the crystalline *methiodide* (VI), m. p. 218° (decomp.). Yield, 1·5 g. It can also be prepared directly from the resin. The resin (3·028 g.) was dissolved in methyl iodide and the solution warmed. After 12 hours the crystals, which had separated, were triturated with acetone, filtered off, and dried. Yield, 0·7 g. It was recrystallised from methyl alcohol; m. p. 218° (decomp.) (Found: C, 30·6; H, 5·3; N, 8·4; I, 39·7;

NO_2, 15·4. $C_8H_{17}O_3N_2I$ requires C, 30·4; H, 5·4; N, 8·9; I, 40·2; NO_2, 14·6%). With picric acid it gave the corresponding *picrate*, m. p. 210°, after recrystallisation from water (Found: C, 40·4; H, 4·5; N, 16·8. $C_{14}H_{19}O_{10}N_5$ requires C, 40·4; H, 4·1; N, 16·8%).

An aqueous suspension of silver oxide (10 g.) converted the methiodide (1·775 g.) into the hydroxide of (VI) (1·2 g.) which, on distillation, decomposed violently, giving various liquid and gaseous products. The distillate was strongly alkaline and had a pronounced odour resembling that of methylamine. Addition of picric acid to a solution of the gaseous products absorbed in dilute hydrochloric acid gave a pale yellow picrate soluble in water and alcohol and almost insoluble in dilute hydrochloric acid; m. p. 156°. It was identified (by mixed m. p.) as dimethylamine picrate. The liquid distillate contained an aldehyde or ketone, which formed a 2 : 4-*dinitrophenylhydrazone*, m. p. 166° (Found: C, 49·8; H, 4·2; N, 21·6. $C_{11}H_{14}O_4N_4$ requires C, 49·6; H, 5·3; N, 21·1%), and a base, which, with methyl iodide, gave a derivative, m. p. >300°.

Decomposition of the Hydrochloride of (V).—When the hydrochloride of (V) was boiled with water, formaldehyde (1 mol.) was evolved (Found: CH_2O, 14·1. 1 mol. of CH_2O requires 15·2%). On evaporation of the aqueous solution, the *hydrochloride* of 2-nitro-2-hydroxymethylbutylamine (III) remained. It is a crystalline solid, very soluble in alcohol, acetone, and water, sparingly soluble in ether, m. p. 126°, and is the final product of decomposition of the more complex bases (VIII), (X), (V), and (VII). No crystalline picrate or methiodide could be prepared. It was recrystallised from propyl alcohol; m. p. 126° (Found: C, 32·6; H, 7·0; N, 14·1; Cl, 19·5. $C_5H_{12}O_3N_2$,HCl requires C, 32·7; H, 6·8; N, 15·2; Cl, 19·3%).

The hydrochloride of (III) (1 g.) reacted with the calculated quantity of sodium nitrite dissolved in water (5 c.c.). A colourless gas was evolved, briskly at first and then more slowly; the solution became slightly milky and heat was evolved. Total volume of gas at N.T.P., 145 c.c. (Found: N_2, 67·6; NO, 1·8; N_2O, 24·1; CO_2, 5·5; CO, 1·0%). This reaction occurred, if only 0·25 mol. of sodium nitrite was added. Addition of urea failed to prevent the second part of the reaction from occurring, once nitrogen had been evolved. The yellow-green oil which separated had an odour resembling that of diazomethane. The oil (0·43 g.) was extracted with ether and distilled under reduced pressure. Much decomposition occurred and a yellow acidic oil (0·1 g.) passed over, $n_D^{18°}$ 1·4700, b. p. 140° (bath temp.)/0·01 mm. (Found: C, 45·6; H, 7·4; N, 8·9%). Formaldehyde was liberated on boiling the hydrochloride of (III) with sodium hydroxide (Found: CH_2O, 11. One mol. requires CH_2O, 16·2%).

The oily *base* (III) was obtained by ethereal extraction of a solution of the hydrochloride made alkaline. Evaporation of dried extracts under reduced pressure gave a syrup which evolved ammonia on standing with formation of crystals. The crystals were basic, m. p. 98° depressed on admixture with (VIII) or (IX) (Found: C, 39·1; H, 7·1; N, 13·1. $C_5H_{12}O_3N_2$ requires C, 40·4; H, 7·7; N, 13·5%). This crystalline substance gave no test for primary or secondary nitro-groups. It was insoluble in ether. It gave ammonia with alkalis, whilst with concentrated alcoholic hydrogen chloride it gave formaldehyde and the hydrochloride of (III), m. p. 126°.

A sample of the mother liquor, after removal of the crystalline derivative, m. p. 98°, gave with concentrated hydrochloric acid a mixture of the hydrochloride of (V), m. p. 203° (decomp.), and the hydrochloride of (III), m. p. 126°. After removal of the base (III) by ether extraction, the mother liquors, on heating, gave an oily *base* with a piperidine-like odour. This was extracted with ether and the dried extracts were evaporated. The strongly alkaline oil (10% yield calculated on the weight of hydrochloride) was distilled under reduced pressure; b. p. 160°/16 mm., $n_D^{22°}$ 1·4862 (Found: C, 46·8; H, 8·1; N, 20·4. $C_{10}H_{20}O_4N_4$ requires C, 46·2; H, 7·7; N, 21·6%). The oil gave no crystalline picrate or methiodide. The oily methiodide contained 34·8% of iodine.

Characteristic Reaction for Bases (VIII) *and* (IX) *and their Derivatives* (VII) *and* (X).—The substance [(VIII), (IX), (VII), or (X)] was shaken with bromine dissolved in carbon tetrachloride; alcohol was added to produce a clear solution followed by the addition of alcoholic potassium hydroxide. The solution lost its bromine colour and became pink–red. The addition of a drop of acid deepened the colour but excess changed it to yellow. Addition of potassium hydroxide brought back the red colour. The base (V), its methiodide (VI), and the base (III) did not give this reaction.

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173. *Some Catalysed Gas-phase Reactions of Aromatic Hydrocarbons. Part I. The Interaction of Benzene with Methyl Ether.*

By P. H. GIVEN and D. LL. HAMMICK.

Methyl ether interacts with benzene at 400—500° in the presence of metal oxide catalysts to give toluene and polymethylbenzenes. The most effective catalysts are of the synthetic aluminosilicate type. The reaction has been investigated under various conditions of temperature, contact time, etc.; the gaseous products have been determined. Under the optimum conditions for the reaction, 12—15% (moles) of toluene per pass is formed, or 35—50% calculated on the benzene consumed; the total methylation (on benzene consumed) is about 70%. Wastage of the rectants is low.

The results obtained are compared with those of previous work, and the nature of the reaction is briefly discussed.

THE various known methods for alkylating aromatic hydrocarbons in solution, *e.g.*, the Friedel–Crafts reaction and its modifications, have been thoroughly investigated (see, *e.g.*, Calloway, *Chem. Reviews*, 1935, **17**, 327; Linstead, *Ann. Reports*, 1937, **34**, 254); they have been very widely applied, and their mechanisms have been elucidated. In recent years, several processes for the production of certain alkylbenzenes in the gas phase have been reported, but gas-phase alkylation as a general method has not been investigated nearly so extensively as the corresponding reaction in solution, and available data on the reactions which have been studied are limited in scope.

The catalytic ethylation of benzene by means of ethanol or ethylene in the gas phase is a reaction now widely used in the United States in the manufacture of ethylbenzene (and hence styrene) for the production of plastics and synthetic rubber (Anon., *Oil and Gas J.*, 1942, **41**, No. 13, 14). Kieselguhr, impregnated with phosphoric acid, and aluminium silicates are suitable catalysts (see, *e.g.*, Standard Oil Co., U.S.PP. 2,238,594, 2,390,211, 2,067,764; Ipatieff and Schmerling, *Ind. Eng. Chem.*, 1946, **38**, 400; Pardee and Dodge, *ibid.*, 1943, **36**, 273). Other olefins, such as propene and the butenes, or alcohols or ethers which can give rise to them, have been used in similar processes (see Universal Oil Co., B.P. 464,752, 1935; Ipatieff, Pines, and Schaad, *J. Amer. Chem. Soc.*, 1944, **66**, 816).

The particular case of methylation is of interest, since the reaction cannot proceed by way of an olefin. Methanol, methyl ether, and methyl chloride have been used as methylating agents in gas-phase reactions. For instance, Jenkins (B.Sc. Thesis, Oxford, 1940) observed that when benzene and methanol were passed over bauxite heated to 400°, about 2% of toluene was formed, together with much methyl ether and water. (Other published work is reviewed, and considered in relation to the present work, below, under "Discussion.") It is well known that methanol is rapidly converted into methyl ether and water in the presence of certain metal oxide catalysts: $2CH_3{\cdot}OH = (CH_3)_2O + H_2O$ (see, *e.g.*, Adkins and Perkins, *J. Physical Chem.*, 1928, **32**, 221). Hence, when benzene and methanol vapours are led over a catalyst, it is uncertain whether the alcohol or the ether is the actual reactant.

Our experiments confirm that methyl ether interacts with benzene in the presence of catalysts to give methylbenzenes, and show that water is one of the reaction products. We find that, under the conditions we have employed, the ether is a more effective methylating agent than the alcohol. We obtain yields of toluene comparable with those claimed by previous workers (see p. 933), *viz.*, 15% (moles) per pass, and 35—50% on the benzene consumed, the total methylation (on benzene consumed) being about 70%. (Here and throughout the paper, all yields are given as moles %.) The wastage of methyl ether is 10—15% per pass.

In the present communication we present a study of the interaction of benzene and methyl ether. A number of catalysts have been examined, and the reaction investigated under various conditions of temperature, contact time, etc. The gaseous products of the reaction have been determined. Subsequent communications will describe the isomeric composition of the polymethyl derivatives formed in the methylation of benzene and its homologues, and also the methylation of thiophen and pyridine. Certain catalytic rearrangements and cracking reactions undergone by the aromatic compounds will also be reported later.

EXPERIMENTAL.

The vapours of benzene and methyl ether were led at known and constant rates through an electrically heated horizontal Pyrex tube containing the catalyst. The liquid products were analysed by fractional distillation in a Podbielniak still, and gaseous products were collected and also analysed.

1. *Materials.—Benzene.* "AnalaR" Benzene was purified by crystallisation, and distillation from phosphoric oxide; $n_D^{20°}$ 1·5007—1·5010, m. p. 5·4°.

Methyl ether. This was prepared by passing methanol over alumina at 375°, and collected in sulphuric acid. The ether was regenerated by running the sulphuric acid solution into water, and was dried, liquefied by cooling, and poured into a cylinder while cold. A needle valve was then screwed into the cylinder.

Catalysts. Three naturally-occurring materials have been used as catalysts, *viz.*, two specimens of bauxite, and a Scottish bauxitic clay. Two further catalysts were made by extraction of the bauxitic clay with acids to reduce, first, the alumina (Silica "O"), and secondly, the titania content (Silica "T"). The analyses were as shown in Table I.

Alumina A. Activated alumina, supplied by Peter Spence, Ltd.

Alumina B. "Special activated alumina", supplied by Peter Spence, Ltd.

Alumina C. Prepared by running 8% sodium hydroxide solution into 36% aluminium nitrate solution at 50—55°; 8/14 mesh.

Alumina D. Prepared by precipitation of aluminium nitrate solution with ammonia, by the method of Adkins and Krause (*J. Amer. Chem. Soc.*, 1922, **44**, 385).

Alumina E. Supplied by I.C.I. Ltd.; screened 10/18 mesh.

Ferric oxide. Prepared in the same way as Alumina C.

TABLE I.

	Bauxite A.[1]	Bauxite B.[2]	Natural alumino-silicate.[3]	Silica-"O".[3]	Silica "T."[3]
Loss on ignition, %	22·7	21·7	7	0·78	0·92
Al_2O_3, %	35·6	67·9	41—42	7·44	2·11
SiO_2, %	30·9	0·96	48	85·95	92·06
Fe_2O_3, %	6·9	7·17	1	0·27	0·27
TiO_2, %	4·3	2·83	1—2	4·04	2·52

[1] Traces of Cr, Mn, and SO_4''; analysis made by I.C.I. Ltd.

[2] Trace of Mg; analysis by Dr. Hartley, Inorganic Chemistry Laboratory, Oxford.

[3] The materials and their analyses were supplied by Messrs. Peter Spence Ltd.; all three had been heated to 500° before analysis.

Titania gel. Titanium tetrachloride was run slowly into excess of 10% ammonia.

Silica gel, basic aluminium phosphate, boron phosphate, and thoria gel. Supplied by I.C.I. Ltd.

Chromic oxide gel. A dilute solution of chomic nitrate was precipitated at 78—84° with 17% ammonia solution.

Zinc oxide gel. Zinc chloride solution was precipitated with sodium hydroxide solution (see Adkins and Millington, *J. Amer. Chem. Soc.*, 1929, **51**, 2452).

Nickel–alumina. A method of Balandin and Rubinstein (*Z. physikal. Chem.*, 1935, *B*, **31**, 793) was used. Sufficient 10% sodium hydroxide was run into 0·25M-aluminium nitrate solution just to redissolve the precipitate first formed. An equivalent quantity of nickel nitrate in 0·5M-solution was run in with stirring. After being washed, filtered off, and dried, the product was reduced in hydrogen at 320—340°.

Mixed oxide–silica catalysts. The following mixtures of silica with other oxides were prepared by Dr. W. Cule Davies, of Peter Spence Ltd., by precipitation of sodium silicate solution with an appropriate salt: Al_2O_3–SiO_2, 3 : 1, 1 : 1, 1 : 2, 1 : 4; Cr_2O_3–SiO_2, 1 : 2; TiO_2–SiO_2, 1 : 2; BeO–SiO_2, 1 : 1.

Except where otherwise stated, all materials were screened 4/8 mesh.

2. *Apparatus.*—The rate of flow of methyl ether was measured with a flow-meter; this was calibrated for rates of flow of 0—40 g. (0—20 l.) per hour by absorption in concentrated sulphuric acid and weighing the methyl ether passed in a known time for a known deflection of the flow-meter. The gas was freed from water, carbon dioxide, and methanol by passing through a long tube packed with soda–lime and calcium chloride.

The benzene was vaporised in a Dewar vessel by heating electrically with a small element immersed in the liquid (principle suggested by Adkins, *J. Amer. Chem. Soc.*, 1922, **44**, 2175). Since the insulation provided by a Dewar vessel is not perfect, the apparatus had to be calibrated directly. Benzene could be vaporised conveniently at rates of 15—100 g. per hour.

The vapours were mixed, preheated, and injected into the catalyst chamber, a Pyrex tube 2·9 cm. in diameter; the catalyst column in the evenly heated section of the furnace was 84 cm. long. The tube was heated in an electric furnace whose temperature could be kept constant $\pm 2°$ by suitable adjustment of a rheostat. The temperature was measured with a thermocouple and millivoltmeter. The charge of catalyst was 200—450 g., depending on its bulk density.

The liquid reaction products were collected, separated from water, dried and analysed by fractional distillation.

Podbielniak still used in analysis. Analyses of the liquid products of reaction were made by means of a Podbielniak-type still (column of 0·55 cm. internal diameter); this enabled benzene and its homologues to be separated without difficulty. For instance, 1·5 c.c. of toluene in 20 c.c. of benzene could be determined with a maximum uncertainty of 0·1 c.c., and larger samples were analysed with corresponding or greater accuracy.

Gas analyses. These were performed with the standard Bone and Wheeler apparatus. As absorbents, 86% H_2SO_4, 20% KOH, 20% oleum, and alkaline pyrogallol were used for methyl ether, CO_2, C_2H_4, and O_2 respectively; H_2 and CO were determined by combustion in a copper oxide pipette, and paraffins by explosion.

3. *Method of Working.*—Before use, each catalyst was heated to 500° in a stream of nitrogen; it was then repacked in the tube to ensure that no apppeciable space was left above the solid catalyst. Benzene and methyl ether were passed over the heated catalyst at known rates and for a known length of time. The liquid products (50—100 c.c.) were collected, separated from water, and analysed by fractional distillation. The gaseous products were led through a trap cooled in a freezing mixture of ice and salt (to remove benzene vapour) before collection.

It was found that the activity of the catalysts fell with continued use; hence they were re-activated as necessary by heating in a stream of oxygen for 1—2 hours at 500° (oxides such as Cr_2O_3 which are oxidizable were not so treated).

Results.—1. *Search for active catalysts.* As a primary step, methyl ether was passed with benzene over a heated sample of the specimen of bauxite used by Jenkins (*loc. cit.*) in his experiments with benzene and methanol. The yield of toluene was small (3—5% per pass), although greater than that obtained by Jenkins. Therefore a search for more active catalysts was undertaken.

(i) A preliminary survey of the effect of catalysts on the rate of production of methylbenzenes was carried out in an apparatus of the type used for studying the kinetics of gaseous reactions. Methyl ether was found to be strongly adsorbed on the catalysts examined, and to undergo faster and more complex decomposition than the homogeneous reactions in the gas phase (cf. Hinshelwood and Askey, *Proc. Roy. Soc.*, 1927, *A*, **115**, 215; Staveley and Hinshelwood, *J.*, 1937, 1568). By comparing the pressure–time curves, and the analyses of the gaseous products, obtained when pure methyl ether, and ether plus benzene, were admitted to the apparatus, a qualitative series of catalytic activities was obtained. Alumina B, C, D, and E, ferric oxide, titania, silica, thoria, chromic oxide, zinc oxide, and nickel–alumina

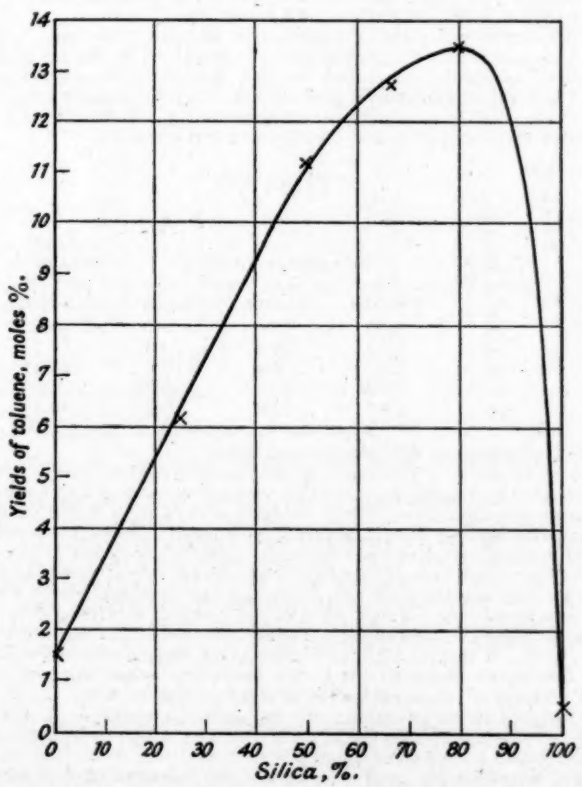
appeared to be ineffective as catalysts. Alumina A, basic aluminium phosphate, and boron phosphate were deemed worthy of further study.

(ii) The search was continued by the flow method described above. In all cases the criterion of the activity of a catalyst was the yield of toluene (moles of toluene as percentage of moles of benzene passed) under the following standard conditions: Vol. of packed catalyst space, 600 c.c.; temp. 450°; rate of flow of benzene, 42 g. per hour; of methyl ether, 12 g. per hour; molar ratio, benzene to ether, 1·8; contact time of benzene 30 secs.; space rate of flow of benzene about 0·15 c.c. of liquid per hour per volume of catalyst. It may be noted that the yield of polymethylbenzene was in all cases less than that of toluene. The average yields under the above conditions are given below in Table II.

TABLE II.

Catalyst.	Yield of toluene (moles %).	Catalyst.	Yield of toluene (moles %).
Bauxite A	4·0	Alumina–silica 1 : 1	11·3
Bauxite B	0·5	,, ,, 1 : 2	13·0
Alumina A	1·5	,, ,, 1 : 4	13·6
Silica	0·5	Chromic oxide–silica	1·7
Boron phosphate	2·0	Titania–silica	5·2
Basic aluminium phosphate	2·7	Beryllia–silica	6·7
Bauxitic clay	4·5	Silica "O"	6·5
Alumina–silica 3 : 1	6·2	Silica "T"	0·8

The plot of yield of toluene against percentage of silica for the alumina–silica mixtures is reproduced in the figure.



Yields of toluene as a function of composition of alumina–silica mixtures.

The mixtures of silica and other oxides are evidently the most effective catalysts, and the 1 : 4 mixture was adopted for all further work.

3. *More detailed investigation of the reaction on alumina–silica catalyst* (1 : 4). Some experiments were made to determine the effect on the reaction between benzene and methyl ether of varying the reaction conditions. The alumina–silica (1 : 4) catalyst was used throughout.

(i) Rate of flow of reactants. The yield of toluene was surprisingly insensitive to variations in the time of contact with the catalyst (see runs 179, 178, 181 in Table III),

TABLE III.

Catalyst: *Alumina–silica* 1 : 4.

Run.	Temp.	Rate of flow (g./hr.). Benzene.	Ether.	Molar ratio, $C_6H_6/C_4H_{10}O$.	Percentage yields of Toluene.	Xylene.	Higher.
179	450°	15·5	7·5	1·1	12·1	4·3	4·1
178	450	42·0	22·9	1·1	12·3	3·8	3·0
181	450	80·0	47·5	1·1	11·0	3·3	3·8
174	450	42·0	7·2	3·4	8·5	—	—
176	450	42·0	15·5	1·6	13·2	4·8	2·7
184	450	42·0	30·0	0·83	13·0	3·3	6·1
186	400	38·5	22·9	1·0	9·1	2·0	3·5
187	400	38·5	12·5	1·9	8·4	1·9	2·9
192*	500	38·5	12·0	1·9	17·3	4·9	2·2
193	500	25·5	22·7	0·65	15·0	5·9	3·2
194	500	27·2	12·0	1·3	15·5	4·0	3·2

* First use of new batch of catalyst.

(ii) Ratio of benzene to ether. It is seen from Table III (runs 174, 176, 184; also 186, 187) that when the rate of flow of benzene is kept constant, an increase in the molar ratio benzene : ether causes only a slight decrease in the yield of methylated products.

(iii) Temperature. The results of experiments at 400° and 500° are given in Table III (runs 186, 187, 192—194). The yields are not markedly temperature-dependent. Experiments over a wider range of temperatures were performed with Bauxite A as catalyst (300—500°). The yield of toluene fell off from 4·0 at 450° to 2·4 at 400°, 1·6 at 350°, and 0·6 at 300°.

(iv) Wastage of reactants, and yields calculated on benzene consumed. In Table IV some representative figures for the recovery of unchanged benzene are given in col. 3; in col. 4, 5, and 6 are given the yields of methylated products calculated on the benzene consumed, *i.e.*, input of benzene less recovered benzene. The total methylation is given in col. 7, the total methylation calculated on the input of benzene in col. 8, and in col. 9 is shown the loss of benzene, *i.e.*, the defect from 100% of the sum of the total methylation (calculated on input) and the benzene recovered.

TABLE IV.

1. Run.	2. Temp.	3. C_6H_6 recovered, %.	4. Percentage yields of Toluene.	5. Xylene.	6. Higher.	7. Total methyln. on C_6H_6 recovered.	8. Total methyln. on C_6H_6 input.	9. % Loss of C_6H_6.
172	450°	68	46·3	15·4	9·0	70·7	22·5	9·5
176	450	71	45·3	16·6	9·4	71·3	20·7	8·3
186	400	68	28·1	6·4	10·9	45·4	14·6	17·4
189	500	73	51·1	13·7	5·2	70·0	19·2	7·8
192	500	65	49·6	14·0	6·2	69·8	24·4	10·6

The wastage of methyl ether per run is estimated below.

4. *Some general observations on the reaction of benzene with methyl ether.* The products of reaction were in all cases pale yellow or orange liquids with a green fluorescence, and contained water (see below). The polymethylbenzenes collected from a large number of runs were found on distillation to contain a small quantity of material boiling above hexamethylbenzene (the polymethylbenzenes will be dealt with more fully in a subsequent communication); this amounted to about 1% of the yield of methylated products, and was possibly a mixture of diphenyl derivatives. Apart from this (and water), no other products than methylbenzenes were detected, except in the methylation of benzene on the beryllia–silica catalyst when methanol was formed, in amount roughly equivalent to the toluene produced. The methanol was separated as its azeotrope with benzene, and characterised by means of its 3 : 5-dinitrobenzoate (m. p. 107°). A certain amount of carbon deposition was observed on all the catalysts.

As already noted, catalysts were reactivated when necessary by heating to 500° in a stream of oxygen for 1—2 hours. The activity of the most active catalyst, alumina–silica (1 : 4), decreased appreciably with continued use, in spite of reactivation; for instance, comparable figures for total methylation (at 500°) are: on a fresh batch of the material, 24%; on one which had been used in 20 previous runs (*i.e.*, *ca.* 800 g. of benzene had passed over it), 19%.

5. *Use of methanol as a methylating agent.* In view of the fact that other workers have used methanol as a methylating agent, it was thought of interest to compare its reaction with benzene with that of methyl ether with benzene, under the same conditions. It was found that methanol is a much less effective methylating agent than the ether; *e.g.*, when basic aluminium phosphate and the alumina–silica (1 : 4) were used as catalysts at 450°, the yields of toluene were ½% and 1% respectively when methanol was the reactant, and 2·7% and 13·0% with methyl ether, for corresponding rates of flow of the reactants. Water and methyl ether were by-products of the reaction of methanol and benzene.

6. *Decomposition of methyl ether.* It was of obvious interest to determine the fate in a methylation experiment of the methyl ether which does not react with benzene. The gaseous products of reaction consist mainly of hydrogen, carbon monoxide, and paraffin, but whereas in the homogeneous decomposition of the ether these products are formed in nearly equal amounts (Hinshelwood and Askey, *loc. cit.*), in

the heterogeneous reaction (in the presence or absence of benzene) they are formed in widely differing proportions in the presence of different catalysts (see Table V). Water was always found in the products of the reaction of benzene with methyl ether, and of the decomposition of the ether alone. When the alumina–silica mixtures were used as catalysts, the ratio of total weight of ether passed to water produced was more or less constant: 1 mole of ether gave about 0·8—1·0 mole of water. Water is therefore one of the products of decomposition of methyl ether on these catalysts. In no case of the surface reaction studied here has it been possible to write a simple stoicheiometric equation between methyl ether and its products of decomposition. Therefore it has not been possible to calculate accurately the wastage of ether in a methylation run from the amount and composition of the gaseous products of reaction. However, from measurements of the volume of gas produced in a known time, during the course of an experiment, and its analysis, the amount of ether decomposed in passage over the catalyst was calculated, on the assumption that the decomposition is accompanied by a trebling of the initial volume. Thus, in the course of a methylation experiment with the alumina–silica (1 : 4) catalyst at 450°, about 10—15% of the ether is decomposed to permanent gases and water; if ether alone is passed over the catalyst the figure is about 20%.

In Table V are presented some representative analyses of the gaseous products resulting from experiments in which (*a*) methyl ether alone, (*b*) methanol alone, and (*c*) benzene plus methyl ether were passed

TABLE V.

Analysis of the gaseous products of reaction.

(All the figures are on a nitrogen-free, ether-free basis, except those for ether itself, which are on a nitrogen-free basis; the analyses are percentage volumes.)

Catalyst.	Temp.	Me_2O.	CO_2.	C_2H_4.	H_2.	CO.	C_nH_{2n+2}.	*n*.
Bauxite A	480°	1·3	5·0	0·4	36·0	24·8	34·7	1·2
" *	480	2·9	3·4	0·4	32·6	26·6	33·8	1·2
Alumina A	440	8·4	0·7	13·3	33·4	18·9	35·0	1·3
" *	440	20·7	2·0	5·3	35·3	22·2	30·8	1·4
Basic Al phosphate	440	16·1	3·3	4·4	8·8	16·8	66·7	1·4
" " †	440	2·7	0·2	1·5	64·7	1·4	32·2	1·25
" " *	440	33·5	16·6	1·9	21·8	25·1	34·6	1·6
" " ‡	440	27·9	4·2	8·4	24·2	29·2	33·6	1·25
Boron phosphate	480	13·6	3·4	5·1	0	8·3	83·3	1·1
" " †	480	3·6	2·3	1·6	0	12·0	84·1	1·4
Thoria	440	2·8	0·8	0·7	70·0	25·1	3·5	1·9
" †	440	0·2	0·7	0·3	76·6	21·2	1·1	—
Bauxitic clay	450	79·7	7·7	3·6	19·9	13·8	55·1	1·5
" " *	450	68·5	16·7	5·9	14·7	11·8	52·0	1·45
Al_2O_3–SiO_2 (1 : 4)	450	0·8	1·0	1·2	4·2	20·4	73·3	1·1
" " *	450	3·2	1·3	2·3	2·7	14·0	7·90	1·1
" "	500	0·6	1·1	0·7	15·4	9·5	73·4	1·1
" " *	500	0·5	0·6	3·0	8·5	7·7	80·0	1·0
BeO–SiO_2	450	67·3	2·6	3·2	10·7	17·2	66·0	1·1

* Products of reaction of benzene and methyl ether.
† Decomposition of methanol.
‡ Products of reaction of benzene and methanol.

Where no sign appears, the figures refer to the decomposition of methyl ether.

over various catalysts. In addition to the observations quoted above, the following points may be noted: (1) The average carbon number, *n*, of the paraffins was nearly always greater than unity. (2) In most cases, the gases had nearly the same composition when (*a*) methyl ether alone or (*b*) methyl ether plus benzene were passed over the same catalyst. (3) A comparison of the decompositions of methanol and methyl ether is interesting: when these substances decompose on the surface of boron phosphate, the gaseous products have nearly the same composition in each case, and the same is true of several other materials which are known to catalyse the conversion of methanol into methyl ether (*e.g.*, alumina, titania, thoria, bauxite, chromic oxide; see Sabatier and Mailhe, *Ann. Chim. Phys.*, 1910, **20**, 298).

DISCUSSION.

The production of toluene by reaction of methanol or methyl ether with benzene at atmospheric pressure is claimed in B.P. 574,738 (Standard Oil Development Co., application dated April 1942; complete specification accepted January 1946 *). The reactants are passed at 300—460° over a catalyst of the " solid " phosphoric acid type, which is prepared by treating a siliceous material (such as clay, kieselguhr, or a synthetic alumina–silica mixture) with a phosphoric acid. Yields of up to 50 moles of toluene per mole of benzene consumed are claimed, though it is not clear how these are calculated from the figures presented. The yields of toluene

* It appears that the work which led to this and the following patent specification was being carried out simultaneously with the work described here, which, with that to be described in subsequent papers of the series, was performed in 1940—1944 and was submitted in 1944 in a thesis for the degree of D.Phil., Oxford, by one of us (P. H. G.).

obtained by us are of comparable magnitude. Our optimum temperature range, 450—500°, is higher than that quoted for the above process (*i.e.*, 325—425°). Methanol is a more effective methylating agent in the Standard Oil Co. process than methyl ether; comparable figures are (for a reaction temperature of 354—358°): 12·2% (moles) of toluene per pass for methanol, and 7·9% for methyl ether as reactant (we obtained 1% and 11·0% respectively at 450° for approximately the same space rate of flow, using the alumina–silica catalyst).

A similar process has been patented by the Gas Light and Coke Co. (B.P. 541,534, application dated 1942), which involves bringing a (4 : 1 molecular) mixture of benzene and methanol at 250—600° (480°) and 100—300 atm. into contact with a phosphoric acid (H_3PO_4) or a metal (magnesium) phosphate alone or on an inert support, *e.g.*, coke, charcoal, siliceous material. The yield of toluene claimed is 14% by volume (12·2 moles %) on benzene passed. A further patent of the same company (B.P. 577,314, application dated March 1942, complete specification accepted May 1946) covers the use of methyl ether in a similar process, virtually the same reaction conditions being employed; the yield of toluene claimed is 18% per pass (15·5% moles), xylenes 4%, polymethylbenzenes 4%, *i.e.*, methyl ether is a more effective methylating agent than methanol in this process. The process uses roughly the same reaction temperatures as ours and gives similar yields, but requires the application of 100—300 atm. pressure.

Cullinane and Chard (*J.*, 1945, 821) have described the interaction of phenol and methanol on alumina at 200—375° to give anisole, homologues of phenol, and hexamethylbenzene.

Kutz and Corson (*J. Amer. Chem. Soc.*, 1945, **67**, 1312) have described the methylation of benzene, toluene, and naphthalene with methyl chloride at 400° over alumina, alumina–silica mixtures, and other materials. In the reaction of benzene on alumina they claim yields of 8—15% (moles) of toluene, which are similar to ours obtained by the use of methyl ether. For their reaction, they find alumina a more active catalyst than the synthetic aluminosilicates.

It is noteworthy that in all these processes for the methylation of benzene, monomethylation predominates, and our work confirms this. This characteristic of the gas-phase reaction is in marked contrast to the property of the Friedel–Crafts method, *viz.*, that the monomethyl product is always accompanied by large quantities of polymethyl derivatives. In fact, the latter method is of little value for preparing monoalkylbenzenes.

Comparison of Methanol and Methyl Ether.—It is of interest to enquire whether, when toluene is produced by passing methanol and benzene over a catalyst, the methanol reacts directly, or first gives methyl ether, which then reacts with benzene. Previous workers (see above; and Cullinane and Chard, *loc. cit.*) do not appear to have envisaged the latter possibility. Our results show that, at least under the conditions we have used, methanol very probably acts as a methylating agent only by virtue of its ready conversion into methyl ether. Thus, we find that the ether gives a much better yield of toluene in reaction with benzene than does methanol. On many catalysts the decomposition products of methanol, produced under the same conditions as obtain in the course of a methylation, have very nearly the same composition as those of methyl ether on the same catalyst; this must mean that the alcohol is rapidly converted into the ether and water, and the ether then decomposes to the final products. In this connection, it may be mentioned that McKee and Burke (*Ind. Eng. Chem.*, 1923, **15**, 793) have shown that the equilibrium between methanol, methyl ether, and water is rapidly achieved at 350° on alumina, and have determined the equilibrium constant at that temperature.

It may be noted that at the temperatures used in methylation experiments, the equilibrium constant of the methanol–methyl ether conversion is of the order of magnitude unity. Given (*J.*, 1943, 589) has obtained:

$$2CH_3{\cdot}OH\ (v) = (CH_3)_2O + H_2O\ (v) : \log_e K_p = 7300/RT - 4{\cdot}8$$

The values of $\log_{10} K_p$ at various relevant temperatures, calculated from this equation, are given in Table VI. The equilibrium constant is actually unity at 761° K. (488° C.). Of course, if the

TABLE VI.

Equilibrium constants of methanol–methyl ether conversion.

Temp., ° K.	300	400	500	600	700	800	900	1000
$\log_{10} K_p$	3·21	19·8	1·09	0·56	0·19	−0·10	−0·32	−0·50

methyl ether produced decomposes, or reacts with benzene, the equilibrium will be shifted by a mass-action effect.

The Metal Oxide–Silica Catalysts.—Our experiments show that the mixed oxide catalysts are all more active than any of the pure oxides examined and that the catalytic activity of the

alumina–silica mixtures varies in an apparently rational way with composition (see Fig.). One would expect there to be some characteristic physical property which distinguishes these materials from the pure oxides, and which varies in a rational manner in a series of mixtures with composition; it is not immediately apparent what that property is. It may be noted that synthetic alumina–silica mixtures have found wide application recently in catalysing many reactions of hydrocarbons, such as polymerisation, isomerisation, and cracking (see, *e.g.*, Nikolaeva and Frost, *Bull. Acad. Sci. U.R.S.S.*, Cl. Sci. Tech., 1944, 536; Thomas, *Ind. Eng. Chem.*, 1945, **37**, 543).

Nature of the Reaction between Methyl Ether and Benzene.—The simplest equation which can be written to represent the reaction of benzene and methyl ether to give toluene is

$$C_6H_6 + (CH_3)_2O = C_6H_5{\cdot}CH_3 + CH_3{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

presumably followed by

$$2CH_3{\cdot}OH = (CH_3)_2O + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

These can be combined into

$$2C_6H_6 + (CH_3)_2O = 2C_6H_5{\cdot}CH_3 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

As stated above, the only reaction products we have detected are methylbenzenes, water, and permanent gases. The gases have virtually the same composition as the decomposition products of methyl ether determined in separate experiments on the same catalyst. It is logical to assume, therefore, that the gases produced in the reaction of benzene and methyl ether are not primary products, but result only from secondary cracking of the ether.

With one exception (the beryllia–silica mixture), we have never found methanol in the reaction products of benzene and methyl ether; in view of the known readiness of reaction (2) this is not surprising. Thus the available analytical data are in accordance with the suggestion that reaction (1) represents the course of the interaction of benzene and methyl ether, but are not sufficient to establish this unequivocally.

Thermodynamic Considerations.—It was thought of interest to determine how nearly the yields of toluene so far obtained approach the theoretical equilibrium values. We have calculated the thermodynamic equilibria in both reactions (1) and (3) above.

The change in heat capacity in both reactions is small over the relevant range of temperatures, and so the heats of reaction were taken as independent of temperature. Considering all the reactants in the gaseous state, we obtain :

Reaction (1) : $\Delta H^\circ_{298\cdot16} = -10{\cdot}23$ kcals.; $\Delta G^\circ_{298\cdot16} = -11{\cdot}68$ kcals.
and $\Delta G^\circ = -10{,}230 - 4{\cdot}86T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$

Reaction (3) : $\Delta H^\circ_{298\cdot16} = -27{\cdot}89$ kcals.; $\Delta G^\circ_{298\cdot16} = -29{\cdot}525$ kcals.
and $\Delta G^\circ = -27{,}890 - 5{\cdot}48T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$

We see from equations (4) and (5) that the free-energy changes of both reactions are always negative. Values of the equilibrium constants are given in Table VII.

TABLE VII.

T ° K.	298·16.	500.	723.	1000.
Reaction (1) $\log_{10} K_p$	18·2	5·50	4·13	3·28
Reaction (3) $\log_{10} K_p$	21·5	13·31	9·57	6·25

We conclude from the data here presented that, thermodynamically, the conversion of benzene into toluene by reaction with methyl ether approaches 100%, and is far larger than that so far observed experimentally. (The data employed were obtained from Pitzer and Scott, *J. Amer. Chem. Soc.*, 1943, **65**, 803; Prosen, Gilmont, and Rossini, *J. Res. Nat. Bur. Stand.*, 1945, **34**, 65; Bichowsky and Rossini, " Thermochemistry of some Chemical Substances "; Crawford, *J. Chem. Physics*, 1943, **8**, 526; Given, *loc. cit.*).

The authors wish to express their gratitude to Dr. E. H. Rodd and Dr. Green of I.C.I. (Dyestuffs) Ltd. for helpful discussions and gifts of materials for use as catalysts; Dr. W. Cule Davies and Messrs. Peter Spence Ltd. for the preparation of the metal oxide–silica catalysts, which was specially undertaken; and the Department of Scientific and Industrial Research for grants to one of them (P. H. G.).

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174. *Curare Alkaloids. Part VI. Alkaloids from* Chondrodendron tomentosum *R. and P.*

By Harold King.

d-Tubocurarine chloride is of value in anæsthesia. The discovery of its botanical origin to ensure future supplies is therefore of importance. *Chondrodendron tomentosum* Ruiz and Pavon has been examined and found to yield *l*-curine and l-*tubocurarine chloride*. Dutcher (*J. Amer. Chem. Soc.*, 1946, **68**, 419) has also examined tube-curare prepared on the Upper Amazon from *Ch. tomentosum* but found *d*-tubocurarine chloride, *l*-curine, and other non-quaternary bases. It is possible that undifferentiated species are covered by the name *Ch. tomentosum*.

In 1935 it was shown (King, *J.*, 1381) that the active principle of tube-curare of native origin was crystalline *d*-tubocurarine chloride. The botanical origin of the poison was not known, but the view was expressed that the genus *Chondrodendron* was probably involved. It was also known, from museum specimens and from the exploratory journeys of Poeppig in the early years of the last century, that tube-curare came from the upper waters of the Amazon in Peru. Through the kind co-operation of Mr. J. W. Massey of the British Consulate at Iquitos in Peru, I received in 1939 a quantity of the liane, " amphi huasca " (amphi = poison, huasca = rope), used by the Indians near Tarapoto in the preparation of curare, which was collected by the late Guillermo Klug. At the same time I also received ample specimens of the leaves of the same liane, and these were identified by Mr. N. Y. Sandwith, M.A., of The Herbarium, Kew, as being indistinguishable from the leaves of *Ch. tomentosum* R. and P. They agreed perfectly with leaves (herbarium sheet No. 4474) collected by Spruce at Tarapoto in 1856 and identified as *Ch. tomentosum* by Moldenke (Krukoff and Moldenke, *Brittonia*, 1938, **3**, 16).

The powdered stem was extracted with dilute tartaric acid; a sample of the neutralised extract had a true curare action when tested on the frog. The extract was worked up for non-quaternary and quaternary alkaloids in the usual way; the non-quaternary fraction readily yielded *l*-curine (*l*-bebeerine) identical with the alkaloid isolated from natural tube-curare (King, *loc. cit.*). The quaternary fraction crystallised with difficulty but was eventually obtained pure and proved to be, not *d*-tubocurarine chloride as expected, but l-*tubocurarine chloride*.

Folkers and Unna (*Arch. int. Pharmacodyn.*, 1939, **61**, 373) examined a small specimen of *Ch. tomentosum* collected by Klug and identified by Krukoff, and found evidence of definite curare-like action in the crude quaternary fraction. Wintersteiner and Dutcher (*Science*, 1943, **97**, 467; Dutcher, *J. Amer. Chem. Soc.*, 1946, **68**, 419), however, were able to examine a sample of curare, prepared by Indians of the Upper Amazon, in which only one plant species was used. This was said to have been identified as *Ch. tomentosum* by a botanist at the time of preparation and authenticated by herbarium specimens. From this curare they isolated four non-quaternary bases, one of which was identified as *l*-curine, and a quaternary crystalline alkaloid which proved to be *d*-tubocurarine chloride.

The conclusion to be drawn from these observations, provided the botanical identification of the raw materials has been correct, is that under the name *Ch. tomentosum* there must be two closely allied species which need further differentiation by systematic botanists, one of which yields *l*-curine and *l*-tubocurarine chloride and the other *l*-curine and *d*-tubocurarine chloride. The position is reminiscent of that which held for " pareira brava " until a few years ago (King, *J.*, 1940, 737). Sometimes this drug gave *d*-bebeerine and sometimes *l*-bebeerine, and this was traced to the fact that two closely allied and difficultly distinguishable *Chondrodendron* species were concerned, one of which, *Ch. microphyllum*, gave *d*-bebeerine and the other, *Ch. platyphyllum*, *l*-bebeerine. It is not without interest that *Ch. toxicoferum* (Wedd, Krukoff and Moldenke) (*Ch. polyanthum*, Diels) bears a superficial resemblance to *Ch. tomentosum* and grows like the latter in the Huallaga river valley of the Upper Amazon. Chemical examination of this species is much to be desired.

Experimental.

The stem of *Ch. tomentosum* (667 g.) was powdered and percolated with 1% tartaric acid (10 l.) and the solution then concentrated to 1 l. This solution when neutralised was tested for curare activity on the frog; the paralysing dose corresponded to 1·0 g. of stem per kg. of frog (compare King, *J.*, 1937, 1478, for definition).

A preliminary assay for alkaloidal content and distribution of activity was carried out on the main solution. Of this, 10 c.c. were treated with chloroform (50 c.c.) and saturated sodium hydrogen carbonate solution (15 c.c.). An amorphous precipitate which formed was removed by filtration, and the aqueous layer was extracted with 3 further portions of chloroform. The chloroform on evaporation

left a syrup which on being moistened with methyl alcohol crystallised, yield 0·5 g. This proved to be *l*-curine, m. p. 213°. The rotation of the dried material was determined in N/10-hydrochloric acid; $[\alpha]_{5461}$ − 313°. Pure *l*-curine under similar conditions gave $[\alpha]_{5461}$ − 340° (King, *J.*, 1940, 742). The rotation liquor on evaporation readily crystallised giving *l*-curine hydrochloride, m. p. 282° (efferv.) not depressed by admixture with pure *l*-curine hydrochloride.

The sodium hydrogen carbonate mother liquor and the amorphous precipitate, which had been collected, were separately neutralised with sulphuric acid and assayed by the frog test. It was found that there was approximately twice as much activity in the precipitate (phenolic betaine formation) as in the mother liquor.

On this basis, the main bulk of solution was worked up in a similar way. The total yield of crystalline *l*-curine was 34·1 g. corresponding to a 5% yield on the original stems.

The combined amorphous precipitates produced by bicarbonate and insoluble in chloroform were dissolved in N/10-sulphuric acid, concentrated to 1150 c.c., and treated with sulphuric acid (57 g.) followed by 25% phosphotungstic acid in 5% sulphuric acid. The precipitate was converted into the hydrochloride in the usual way, and the solution concentrated to 70 c.c. and treated with saturated aqueous mercuric chloride solution (70 c.c.) followed by addition of solid mercuric chloride (15 g.). The precipitate was decomposed with hydrogen sulphide and the filtered solution evaporated to dryness, yield 5·7 g. (*A*).

In a similar way the sodium hydrogen carbonate mother liquor was neutralised, concentrated to 800 c.c., precipitated with phosphotungstic acid solution, converted into chloride, and precipitated with mercuric chloride. The mercury-free water soluble residue amounted to 5·6 g. (*B*).

These two fractions of comparable weights, containing the quaternary alkaloids, were kept as aqueous syrups at 0° for some months; that from the amorphous phenolic-betaines (*A*) had then crystallised partially. The solid was collected, yield 0·74 g. It was crystallised twice from water and gave l-*tubocurarine chloride*, minute needles, m. p. 275° (efferv.) (Found on hydrated material: loss at 100° (macro), 10·7; (micro), 9·6. OMe (micro), 7·0. $C_{38}H_{44}O_6N_2Cl_2,5H_2O$ requires H_2O, 11·5; loss of $4H_2O$, 9·2; 2OMe, 7·9%. Found on dried material (micro): C, 63·5; N, 6·5. $C_{38}H_{44}O_6N_2Cl_2,H_2O$ requires C, 63·9; H, 6·5%). Partial loss of water of crystallisation on micro-drying had been observed previously for *d*-tubocurarine chloride (King, *J.*, 1935, 1386). The anhydrous salt showed $[\alpha]^{20°}_{5461}$ − 258° (*c*, 0·38). The rotation of *d*-tubocurarine chloride was determined afresh under comparable conditions and gave $[\alpha]^{20°}_{5461}$ + 256° (*c*, 0·39) for the anhydrous salt.

The mother liquors of the *l*-tubocurarine chloride were fractionally precipitated with saturated aqueous mercuric chloride and seven fractions collected. Each of these was freed from metallic ions, but no further crystallisation of *l*-tubocurarine chloride could be effected. Each of these fractions was then completely methylated in methyl alcoholic solution with methyl iodide in excess and sodium methoxide, and each gave complex amorphous quaternary iodides. From fraction 6 a crystalline solid was obtained which on further crystallisation from water gave l-O-*methyltubocurarine iodide* clusters of small prisms, m. p. 268° (efferv.), yield 22 mg. (Found: Loss at 95°, 5·5. $C_{40}H_{48}O_6N_2I_2,3H_2O$ requires H_2O, 5·6%. Found for the anhydrous salt: C, 51·7; H, 5·6; OMe, 13·8. $C_{40}H_{48}O_6N_2I_2$ requires C, 52·9; H, 5·3; 4OMe, 13·7%). The figure for carbon is low but the same figure was found in duplicate micro-analyses of the dextro-form (King, *J.*, 1935, 1386). *d-O*-Methyltubocurarine iodide had previously been found to melt at 266—267° (efferv.).

It is probable that the *l-O*-methyltubocurarine iodide has arisen from *l*-tubocurarine chloride present in the mother liquors.

The fraction, 5·6 g. (*B*) above, failed to give *l*-tubocurarine chloride by direct crystallisation. It has not been examined further chemically, but biological assay showed that it contains a more powerful curarising agent than *l*-tubocurarine chloride.

I am indebted to Dr. B. D. Burns of this Institute for a biological assay of *l*-tubocurarine chloride, which, on the isolated rat's diaphragm, was 30 to 60 times weaker than *d*-tubocurarine chloride. The quaternary fraction (*B*) was about 3·5 times weaker than *d*-tubocurarine chloride, but the active principle contained in it cannot be *d*-tubocurarine chloride.

My thanks are also due to Mr. F. J. Pound, Agronomist to the Department of Agriculture of Trinidad, for help in securing *Ch. tomentosum* whilst in Peru.

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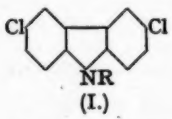
175. *The Friedel–Crafts Reaction in the Carbazole Series. Part III.*

By S. G. P. PLANT and (MRS.) J. F. POWELL.

3 : 6-Dichloro- and 3 : 6-dibromo-9-acetylcarbazole were recovered largely unchanged in attempts to apply Friedel–Crafts reactions, but the closely related 6-chloro-9-acetyltetrahydrocarbazole readily gave its 7-*acetyl* derivative under similar conditions. 6-*Bromo*-9-*acetyl*- and 9-acetyl-6-methyl-tetrahydrocarbazole gave analogous products, but several unacetylated tetrahydrocarbazoles proved to be unreactive. 3 : 6-Dichlorocarbazole, which has been prepared synthetically from 5 : 4′-*dichloro*-1-*phenylbenzotriazole*, gave only *N*-acyl derivatives.

IT has been established that under the usual conditions for Friedel–Crafts reactions two acyl groups can be readily introduced into carbazole and its 9-alkyl derivatives in the 3- and the

6-position, but with the 9-acylcarbazoles substitution of a single acyl group in the 2-position ensues (*J.*, 1935, 741; 1936, 1295). It seemed possible that these reactions might be extended to the preparation of substances which would be of value as intermediates for dyes by the use of certain substituted carbazoles, *e.g.*, 3 : 6-dichloro-9-acetylcarbazole (I; R = Ac). 3 : 6-Dichlorocarbazole was first prepared by Mazzara and Lamberti-Zanardi (*Gazzetta*, 1896, **26**, 236) by heating carbazole with sulphuryl chloride in chloroform, but the constitution of the product appears never to have been rigidly established. This has now been achieved in the form of an unambiguous synthesis by heating 5 : 4′-*dichloro*-1-*phenylbenzotriazole* (II) (the Graebe–Ullmann reaction), which was obtained from 4 : 4′-dichloro-2-nitrodiphenylamine through the corresponding 2-amino-compound.



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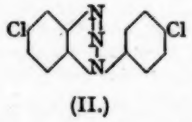

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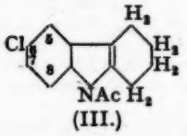

(III.)

3 : 6-Dichloro-9-acetylcarbazole proved to be unreactive towards acetyl bromide and aluminium chloride in boiling carbon disulphide. Similar lack of reactivity was displayed towards phthalic anhydride and aluminium chloride in nitrobenzene, except that in one experiment, after prolonged standing, a very small quantity of 3 : 6-*dichlorocarbazole*-9-*phthaloylic acid* (I; R = $CO{\cdot}C_6H_4{\cdot}CO_2H$), formed by displacement of the acetyl group, was isolated. 3 : 6-Dichlorocarbazole itself reacted with phthalic anhydride, benzoyl chloride, and acetyl chloride in the presence of aluminium chloride with the introduction of the corresponding acyl radical, but the substituent was shown in each case to be attached to nitrogen by the fact that it could readily be removed by warming with alkali, and *C*-acylation was not observed. 3 : 6-Dibromo-9-acetylcarbazole also failed to react with acetyl bromide under similar conditions.

In contrast, it was found that the closely related 6-chloro-9-acetyltetrahydrocarbazole (III) could be easily converted into 6-*chloro*-7 : 9-*diacetyltetrahydrocarbazole*. This was hydrolysed to 6-*chloro*-7-*acetyltetrahydrocarbazole*, the constitution of which was established by reducing it with the Clemmensen reagent. The product, evidently a mixture of 6-chloro-7-ethyltetrahydrocarbazole and 6-chloro-7-ethylhexahydrocarbazole from the fact that it was only partly soluble in dilute acids, was heated with palladised charcoal in an atmosphere of hydrogen with the formation of 2-ethylcarbazole. The result is in harmony with the observations of Plant and Rogers (*J.*, 1936, 40) who found that the 7-acetyl and 7-benzoyl derivatives were obtained when 9-acetyl- and 9-benzoyl-tetrahydrocarbazole were submitted to Friedel–Crafts reactions with acetyl bromide and benzoyl chloride. It was not, however, possible to obtain an analogous phthaloylic acid from 6-chloro-9-acetyltetrahydrocarbazole by the use of phthalic anhydride.

An acetyl group has been similarly introduced into 6-*bromo*-9-*acetyltetrahydrocarbazole* and 9-acetyl-6-methyltetrahydrocarbazole, the products being evidently 6-*bromo*-7 : 9-*diacetyl*- and 7 : 9-*diacetyl*-6-*methyl-tetrahydrocarbazole* respectively. The latter was hydrolysed to 7-*acetyl*-6-*methyltetrahydrocarbazole*.

A surprising observation is that unacetylated tetrahydrocarbazole, and its 6-chloro-, 6-bromo-, 6-methyl, and 6-acetamido-derivatives, were recovered unchanged after treatment with acetyl bromide and aluminium chloride in carbon disulphide, even with prolonged boiling. This is remarkable in view of the ease with which carbazole undergoes substitution.

Experimental.

Synthesis of 3 : 6-*Dichlorocarbazole*.—After a mixture of 2 : 5-dichloronitrobenzene (16 g.), *p*-chloroaniline (12 g.), and potassium carbonate (12 g.) had been heated at 220° for an hour, unchanged materials were removed in steam and the residue crystallised from alcohol, 4 : 4′-dichloro-2-nitrodiphenylamine being obtained in crimson needles, m. p. 149—150° (cf. Blom, *Helv. Chim. Acta*, 1921, **4**, 1038). The nitro-compound (1·2 g.) in hot glacial acetic acid (20 c.c.) was treated gradually with stannous chloride (6 g.) dissolved in hydrochloric acid (20 c.c. of 28%), and the solution boiled for 10 minutes, cooled, and made alkaline with concentrated aqueous potassium hydroxide. The precipitated amine separated from alcohol in colourless needles, m. p. 137°. Its suspension in glacial acetic acid was treated with aqueous sodium nitrite, and, after the addition of water, the precipitated 5 : 4′-*dichloro*-1-*phenylbenzotriazole* was crystallised from alcohol and obtained in brown needles, m. p. 175° (Found : N, 15·9. $C_{12}H_7N_3Cl_2$ requires N, 15·9%). When this substance was heated for an hour at 360° and the product distilled under reduced pressure, 3 : 6-dichlorocarbazole, colourless prisms, m. p. 202°, from glacial acetic acid, was obtained. It proved to be identical (mixed m. p.) with the material obtained by the chlorination of carbazole as described by Mazzara and Lamberti-Zanardi (*loc. cit.*).

Attempted Friedel–Crafts Reactions with 3 : 6-*Dichlorocarbazole*.—(*a*) A solution of 3 : 6-dichlorocarbazole (2 g.), phthalic anhydride (2 g.), and aluminium chloride (2 g.) in nitrobenzene (25 c.c.) was left

at room temperature for 4 days and then treated with ice–dilute hydrochloric acid, and the solvent removed in steam. After the residue had been dissolved in hot alcohol and poured into dilute ammonia, the filtered aqueous solution was acidified, and 3 : 6-*dichlorocarbazole-9-phthaloylic acid*, colourless needles, m. p. 185° (rapid heating), from glacial acetic acid, obtained (Found : Cl, 18·2. $C_{20}H_{11}O_2NCl_2$ requires Cl, 18·5%). When its solution in aqueous ammonia was boiled, a precipitate of 3 : 6-dichlorocarbazole, identified by mixed m. p., soon appeared. Similar results were obtained when the reaction was carried out in nitrobenzene at 60° for 6 hours.

(*b*) Benzoyl chloride (2·5 g.) was added to 3 : 6-dichlorocarbazole (2 g.) and aluminium chloride (2·5 g.) in carbon disulphide (25 c.c.), and the whole refluxed for an hour. After the carbon disulphide had been distilled off, the residue poured into ice–dilute hydrochloric acid, and the excess of benzoyl chloride removed in steam, 3 : 6-*dichloro-9-benzoylcarbazole* remained; it separated from glacial acetic acid in almost colourless needles, m. p. 204° (Found : Cl, 20·3. $C_{19}H_{11}ONCl_2$ requires Cl, 20·9%). When its solution in aqueous-alcoholic potassium hydroxide was boiled for 1½ hours and poured into water, 3 : 6-dichlorocarbazole was precipitated.

(*c*) After 3 : 6-dichlorocarbazole had been treated with acetyl chloride and aluminium chloride under conditions similar to those used with benzoyl chloride, 3 : 6-dichloro-9-acetylcarbazole, colourless prisms, m. p. 185°, from glacial acetic acid, was obtained. It was identical (mixed m. p.) with the substance obtained by boiling 3 : 6-dichlorocarbazole with acetic anhydride and a drop of concentrated sulphuric acid under reflux (cf. Mazzara and Lamberti-Zanardi, *loc. cit.*).

6-*Chloro-7-acetyltetrahydrocarbazole*.—Aluminium chloride (2 g.) was added to a mixture of 6-chloro-9-acetyltetrahydrocarbazole (2 g., prepared as described by Plant and Rosser, *J.*, 1928, 2454) and acetyl bromide (1·5 c.c.) in carbon disulphide (30 c.c.), and the whole refluxed for 10 minutes. After the solvent had been distilled off, the residue added to ice–dilute hydrochloric acid, and the solid crystallised from alcohol, 6-*chloro*-7 : 9-*diacetyltetrahydrocarbazole* was obtained in colourless needles, m. p. 118° (Found : C, 66·5; H, 5·2. $C_{16}H_{14}O_2NCl$ requires C, 66·3; H, 5·5%). The reaction proceeded less readily when acetyl chloride was used. When a solution of the diacetyl compound (1 g.) in alcohol (10 c.c.) containing potassium hydroxide (0·6 g.) and water (0·5 c.c.) was refluxed for an hour, filtered, and allowed to cool, 6-*chloro-7-acetyltetrahydrocarbazole* separated. It was recrystallised from alcohol and isolated in almost colourless prisms, m. p. 171° (Found : C, 68·1; H, 6·0; N, 5·9. $C_{14}H_{14}ONCl$ requires C, 67·9; H, 5·7; N, 5·7%).

Acetyl chloride (0·7 c.c. in a little acetone) was gradually added with constant shaking to the 7-acetyl compound (0·5 g.) dissolved in acetone (10 c.c.) containing aqueous potassium hydroxide (0·45 g. of 66%). Water then precipitated 6-chloro-7 : 9-diacetyltetrahydrocarbazole, which was crystallised from alcohol and found to be identical (mixed m. p.) with the substance described above.

Conversion of 6-*Chloro-7-acetyltetrahydrocarbazole into* 2-*Ethylcarbazole*.—6-Chloro-7-acetyltetrahydrocarbazole (2·6 g.) and concentrated hydrochloric acid (50 c.c.) were shaken with amalgamated granulated zinc (200 g.), and the whole was left overnight. After the addition of anisole (5 c.c.) and more concentrated hydrochloric acid (30 c.c.), the mixture was refluxed for 12 hours, the product extracted with ether, the extract evaporated, and anisole removed from the residue by distillation in steam. The less volatile material, which was only partly soluble in dilute acids, was again extracted with ether, and the extract dried (K_2CO_3) and evaporated. When the residue was mixed with 25% of its weight of palladised charcoal and heated at 300—320° for 11 hours in an atmosphere of hydrogen, hydrogen chloride was freely evolved in the early stages. The product was dissolved in warm acetone and recovered from the filtered solution by the addition of water. After it had been distilled under reduced pressure and crystallised from glacial acetic acid, 2-ethylcarbazole was obtained in colourless plates, m. p. 218—220°, identical (mixed m. p.) with the substance prepared by Plant and Williams (*J.*, 1934, 1142).

6-*Bromo*-7 : 9-*diacetyltetrahydrocarbazole*.—After a solution of 6-bromotetrahydrocarbazole (25 g., Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 53) in acetic anhydride (90 c.c.) containing a few drops of concentrated sulphuric acid had been refluxed for 6 hours, 6-*bromo-9-acetyltetrahydrocarbazole* separated on cooling. It was recrystallised from alcohol (charcoal) and obtained in colourless plates (15 g.), m. p. 120° (Found : N, 4·7. $C_{14}H_{14}ONBr$ requires N, 4·8%). Aluminium chloride (4 g.) was added to a mixture of this acetyl compound (2 g.) and acetyl chloride (6 c.c.) in carbon disulphide (25 c.c.), and the whole refluxed for 15 minutes and treated as described for the corresponding chloro-compound. When the product was crystallised from alcohol, 6-*bromo*-7 : 9-*diacetyltetrahydrocarbazole* separated in colourless needles, m. p. 112° (Found : N, 4·2. $C_{16}H_{16}O_2NBr$ requires N, 4·2%). The use of acetyl bromide gave less satisfactory products.

When the diacetyl compound (3 g.) in hot glacial acetic acid (10 c.c.) was treated with concentrated nitric acid (1·2 g.), oxides of nitrogen were evolved, and 6-*bromo*-10 : 11-*dihydroxy*-7 : 9-*diacetylhexahydrocarbazole* separated on cooling. On crystallisation from alcohol, it was obtained in colourless plates, m. p. 210° (decomp.) (Found : C, 52·0; H, 4·9. $C_{16}H_{18}O_4NBr$ requires C, 52·2; H, 4·9%).

7-*Acetyl-6-methyltetrahydrocarbazole*.—When treated with acetyl bromide and aluminium chloride as described for the corresponding chloro-compound, 9-acetyl-6-methyltetrahydrocarbazole (Manjunath and Plant, *J.*, 1926, 2260) gave 7 : 9-*diacetyl-6-methyltetrahydrocarbazole*, colourless needles, m. p. 136°, from alcohol (Found : C, 75·6; H, 7·1. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%). Hydrolysis as for the chloro-compound led to 7-*acetyl-6-methyltetrahydrocarbazole*, colourless plates, m. p. 207°, from alcohol (Found : C, 78·7; H, 7·4. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5%).

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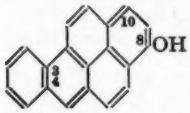
176. *Polycyclic Aromatic Hydrocarbons. Part XXXII. 2′-Methoxy- and 2′-Methoxy-9 : 10-dimethyl-1 : 2-benzanthracene.*

By G. M. Badger.

2′-Methoxy-1 : 2-benzanthracene and *2′-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene* have been prepared by the scheme illustrated in formulæ (V—XII) ,for comparison with the (methylated) metabolic products of 1 : 2-benzanthracene and of 9 : 10-dimethyl-1 : 2-benzanthracene, in rabbits.

In mice and rats, carcinogenic and related polycyclic hydrocarbons are metabolised to phenolic derivatives (I—IV) in which the hydroxy-group occupies the same relative position (Berenblum and Schoental, *Biochem. J.*, 1945, Proc. lxiv). In rabbits, however, 1 : 2 : 5 : 6-dibenzanthracene



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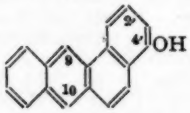

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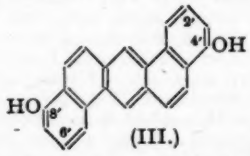

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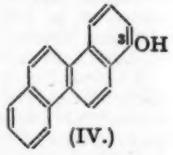


(IV.)

is metabolised to a dihydroxy-derivative which differs from that obtained from mice and rats. This compound has not yet been identified, although several of the 55 possible isomers have been excluded (for references see Cason and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2681; 1941, **63**, 1256). The synthesis of all the remaining isomers would be a difficult task, and the present work was undertaken to provide a clue to the identity of the rabbit metabolite of dibenzanthracene. For this purpose, it was decided to prepare hydroxy-derivatives of 1 : 2-benzanthracene, which could then be compared with the metabolic products of this hydrocarbon, in rabbits. By analogy with dibenzanthracene, it is probable that the rabbit will metabolise benzanthracene to a hydroxy-derivative other than, or in addition to, the 4′-hydroxy-derivative.

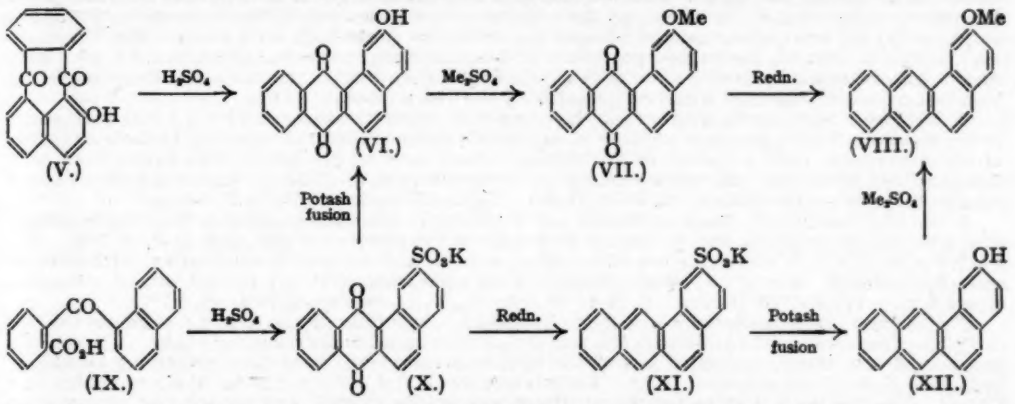
Since rats oxidise benzanthracene and dibenzanthracene at positions which are liable to chemical attack when the *meso*-positions are blocked (Cason and Fieser, *loc. cit.*), it appeared probable that the rabbit would oxidise the same compounds at some other positions which are also liable to chemical attack. In benzanthraquinone, this is the 2′-position, for Joffe and Fedorova (*J. Gen. Chem. Russia*, 1941, **11**, 619) have shown that, at high temperatures, benzanthraquinone is sulphonated at this position. (Other positions of the benzanthraquinone and benzanthracene molecules may also be subject to substitution reactions under certain conditions; see Scholl, *Ber.*, 1911, **44**, 2370; Cook and Hewett, *J.*, 1933, 1408.)

The fact that Berenblum and Schoental (*Cancer Res.*, 1946, **6**, 699) have confirmed the presence of 10-hydroxy-3 : 4-benzpyrene as well as 8-hydroxy-3 : 4-benzpyrene (I) in the excreta of both rats and rabbits, and that more of the 10-hydroxy-derivative is formed in the rabbit, lends added support to this view. For these reasons *2′-methoxy-1 : 2-benzanthracene* and *2′-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene* have been prepared. The comparison of the former with the (methylated) rabbit metabolic products has been undertaken by Drs. Berenblum and Schoental. Such of the compounds as appear to be suitable will be tested for biological action by Professor A. Haddow. Results of these investigations will be published elsewhere.

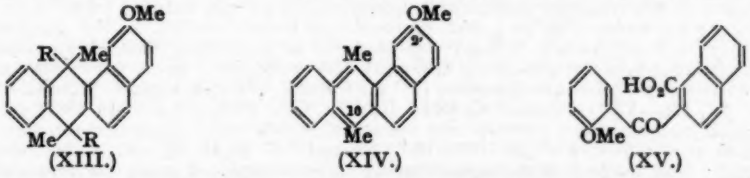
2′-Hydroxy-1 : 2-benzanthracene (XII) was prepared by sulphonation of 2-(1′-naphthoyl)-benzoic acid (IX), followed by reduction and potash fusion, a method substantially the same as that reported by Joffe and Fedorova (*loc. cit.*) except that naphthoylbenzoic acid was used instead of benzanthraquinone. Since the melting point of the final product (XII) did not agree with that reported by the Russian workers (although the melting points of the acetates were substantially in agreement), the scheme outlined in formulæ (V—XII) was carried out.

Phthaloylnaphthol (V) was converted into 2′-hydroxy-1 : 2-benzanthraquinone (VI) by the method of Fieser and Fieser (*J. Amer. Chem. Soc.*, 1933, **55**, 3342). The 50% yield claimed by these authors could not, however, be confirmed. In 35—40 runs, the yield of pure product averaged about 10%. The same compound was also prepared by fusion of potassium 1 : 2-benzanthraquinone-2′-sulphonate (X) with potassium hydroxide by the method of Joffe and Fedorova. Methylation with methyl sulphate gave *2′-methoxy-1 : 2-benzanthraquinone* (VII), which was reduced with stannous chloride, followed by zinc and alkali, to 2′-methoxy-1 : 2-benzanthracene (VIII). The same compound was also prepared by methylation of 2′-hydroxy-1 : 2-benzanthracene obtained following the sulphonation of naphthoylbenzoic acid (IX—XII).

Treatment of 2′-methoxy-1 : 2-benzanthraquinone (VII) with methylmagnesium iodide gave 9 : 10-*dihydroxy*-2′-*methoxy*-9 : 10-*dimethyl*-9 : 10-*dihydro*-1 : 2-*benzanthracene* (XIII,



R = OH). Methylation with methyl alcohol and a trace of sulphuric acid gave 2′ : 9 : 10-*trimethoxy*-9 : 10-*dimethyl*-9 : 10-*dihydro*-1 : 2-*benzanthracene* (XIII, R = OMe), which, on treatment with sodium, gave 2′-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene (XIV) (cf. Bachmann and Chemerda, *J. Org. Chem.*, 1939, **4**, 583; *J. Amer. Chem. Soc.*, 1938, **60**, 1023).



The Friedel–Crafts reaction between phthalic anhydride and β-methoxynaphthalene, in tetrachloroethane solution, is known to give 2-(2′-hydroxynaphthoyl-1′)-benzoic acid or its methyl ether (Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 3546). When nitrobenzene is used as a solvent, the course of Friedel–Crafts reactions between β-methoxynaphthalene and various compounds, especially acyl chlorides, is modified, so that substitution occurs not at the 1-position but at the 6-position (for references, see Hudson, *J.*, 1946, 76). This does not appear to take place with aroyl groups, for Hudson (*loc. cit.*) found that the anisoyl group enters the 1-position. The present work shows that phthalic anhydride also reacts at the 1-position, even in cold nitrobenzene solution. In an attempt to convert 2-(2′-hydroxynaphthoyl-1′)-benzoic acid lactone into 2′-hydroxy-1 : 2-benzanthraquinone with sulphuric acid, only phthaloylnaphthol (V) and phthalic acid were formed. That the CO⁻ bond at the 1-position should be broken under these conditions is of special interest in view of the conversion of phthaloylnaphthol into 1 : 2-benzanthraquinone.

In an attempt to prepare 5-hydroxy-1 : 2-benzanthracene, the Grignard solution from *o*-bromoanisole was condensed with 1 : 2-naphthalic anhydride. Attempts to prepare the benzanthraquinone from the resulting 2-(2′-*methoxybenzoyl*)-1-*naphthoic acid* (XV), by treatment either with sulphuric acid or with benzoyl chloride and a trace of sulphuric acid (Badger and Cook, *J.*, 1939, 802), were unsuccessful.

Experimental.

2′-*Hydroxy*-1 : 2-*benzanthraquinone*.—(i) This was prepared essentially as described by Fieser and Fieser (*loc. cit.*), but the yield claimed could not be confirmed. Phthaloylnaphthol (10 g.) was added to a solution of water (25 c.c.) and sulphuric acid (50 c.c.) and the mixture brought to the boil, with stirring. When oil separated, the mixture was poured on ice (200 g.). The product was extracted with a little boiling alcohol, and some unchanged phthaloylnaphthol filtered off. The crude 2′-hydroxy-1 : 2-benzanthraquinone obtained from the alcohol was dried, and refluxed for 1 hour with acetic anhydride and sodium acetate. The yellow needles which separated on cooling (1·6 g.) gave, on recrystallisation from acetic acid, 2′-acetoxy-1 : 2-benzanthraquinone, m. p. 254—255° (1 g.). The acetic acid liquors yielded colourless plates (0·4 g.) which after purification had m. p. 213—214°. This was evidently acetoxyphthaloylnaphthalene (Found : C, 76·1; H, 3·7. Calc. for $C_{20}H_{12}O_4$: C, 76·0; H, 3·8%). Pure 2′-hydroxy-1 : 2-benzanthraquinone, m. p. 253—253·5°, was obtained from the acetate by hydrolysis with alcoholic sodium hydroxide followed by recrystallisation from alcohol.

(ii) A mixture of 2-(1′-naphthoyl)benzoic acid (15 g.) and concentrated sulphuric acid (150 c.c.) was heated on the water-bath for 1 hour, and then at 150—160° for 6 hours. The dark red solution was poured on ice (150 g.), and the sulphonic acid collected and sucked as dry as possible with the water-pump. The paste was dissolved in hot water, and the solution made alkaline with barium hydroxide. Potassium sulphate (5·1 g.) was added, and the mixture heated on the steam-bath for 2 hours. The filtrate, on evaporation to dryness, gave crude potassium 1 : 2-benzanthraquinone-2′-sulphonate (13·5 g.). After fusion with potassium hydroxide as described by Joffe and Fedorova (*loc. cit.*) this gave 2′-hydroxy-1 : 2-benzanthraquinone, identical with that prepared by the first method.

2′-*Methoxy*-1 : 2-*benzanthraquinone*.—2′-Hydroxy-1 : 2-benzanthraquinone (1·9 g.) was methylated in the usual way by the alternate addition of methyl sulphate and sodium hydroxide, at the temperature of the steam-bath, until a portion of the alkaline filtrate gave no precipitate with hydrochloric acid. Recrystallised from acetic acid, the 2′-*methoxy*-1 : 2-*benzanthraquinone* (1·83 g.) formed long golden-brown needles, m. p. 200—201° (Found : C, 79·3; H, 4·3. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·2%).

2′ : 9 : 10-*Trimethoxy*-1 : 2-*benzanthracene*.—2′-Hydroxy-1 : 2-benzanthraquinone (0·4 g.) was methylated with methyl sulphate and potassium hydroxide in the presence of zinc dust (2 g.) at 100°. The residue after filtration was extracted with boiling alcohol, and the alcohol decolourised with charcoal and concentrated. The 2′ : 9 : 10-*trimethoxy*-1 : 2-*benzanthracene* (0·21 g.) formed almost colourless crystals, m. p. 173·5—175° (Found : C, 79·4; H, 5·4. $C_{21}H_{18}O_3$ requires C, 79·3; H, 5·7%).

2′-*Methoxy*-1 : 2-*benzanthracene*.—(i) 2′-Methoxy-1 : 2-benzanthraquinone (0·25 g.), stannous chloride (1·5 g.), hydrochloric acid (3 c.c.) and acetic acid (5 c.c.) were boiled under reflux for 1 hour. The solution was poured into water, and after 1 hour the solid was transferred to a flask containing 2N-sodium hydroxide (15 c.c.) and zinc dust (1 g.). The mixture was boiled under reflux for 3½ hours, cooled, and filtered. The residue was extracted several times with boiling alcohol, and the solution concentrated and allowed to crystallise. The 2′-*methoxy*-1 : 2-*benzanthracene* (0·1 g.) formed almost colourless flat needles, m. p. 165—166° (Found : C, 88·4; H, 5·3. $C_{19}H_{14}O$ requires C, 88·4; H, 5·4%). The alcoholic solution showed an intense blue fluorescence in daylight.

The *picrate*, prepared in alcohol, formed red-brown needles, m. p. 170—171° (Found : C, 61·9; H, 3·6; N, 8·7. $C_{25}H_{17}O_8N_3$ requires C, 61·6; H, 3·5; N, 8·6%).

(ii) Potassium 1 : 2-benzanthraquinone-2′-sulphonate (7·5 g.) was reduced by 12 hours' boiling with zinc dust (14 g.) in water (300 c.c.) and ammonia (*d* 0·880; 75 c.c.). The resulting potassium 1 : 2-benzanthracene-2′-sulphonate (2·6 g.) was obtained as colourless plates from water. This salt (1·6 g.) was converted into the phenol by fusion at 290—300°, for 1 hour, with potassium hydroxide (8 g.). The 2′-hydroxy-1 : 2-benzanthracene (0·7 g.) formed pale yellow plates from acetic acid, m. p. 191·5—193·5° (lit. 178—179°) (Found : C, 88·5; H, 4·7. Calc. for $C_{18}H_{12}O$: C, 88·5; H, 4·9%). The acetate, prepared by refluxing a portion with acetic anhydride and sodium acetate, formed colourless silky needles, m. p. 156·5—158·5° (lit. 152—153°) (Found : C, 84·1; H, 4·8. Calc. for $C_{20}H_{14}O_2$: C, 83·9; H, 4·9%). The above hydroxybenzanthracene was methylated in almost quantitative yield by the alternate addition of methyl sulphate and sodium hydroxide. The product, crystallised from alcohol, was identical with the 2′-methoxy-1 : 2-benzanthracene prepared by the first method.

2′ : 9 : 10-*Trimethoxy*-9 : 10-*dimethyl*-9 : 10-*dihydro*-1 : 2-*benzanthracene*.—2′-Methoxy-1 : 2-benzanthraquinone (2 g.), suspended in a Soxhlet thimble under the condenser (compare Bachmann and Chemerda, *J. Org. Chem.*, 1939, **4**, 583), dissolved after the Grignard solution [from methyl iodide (3 c.c.), ether (15 c.c.), and benzene (40 c.c.)] had been refluxed for 5 hours. After decomposition with ice-cold ammonium chloride, the organic layer was dried and evaporated. The gummy residue crystallised on stirring with benzene–light petroleum. 2′-*Methoxy*-9 : 10-*dihydroxy*-9 : 10-*dimethyl*-9 : 10-*dihydro*-1 : 2-*benzanthracene* (1·2 g.) formed colourless micro-crystals, from benzene, m. p. 157—160° (decomp.) (Found : C, 78·9; H, 6·3. $C_{21}H_{20}O_2$ requires C, 78·8; H, 6·3%). The *methyl ether* was obtained by dissolving the diol in methyl alcohol and treating the cold solution with sulphuric acid (2 drops) in methyl alcohol (5 c.c.). It formed colourless needles, from methyl alcohol, m. p. 171—172° (Found : C, 79·4; H, 6·9. $C_{23}H_{24}O_2$ requires C, 79·3; H, 6·9%).

2′-*Methoxy*-9 : 10-*dimethyl*-1 : 2-*benzanthracene*.—This was prepared by treatment of the above methyl ether with sodium (cf. Bachmann and Chemerda, *loc. cit.*). Recrystallised from methyl alcohol, 2′-*methoxy*-9 : 10-*dimethyl*-1 : 2-*benzanthracene* formed pale yellow lustrous plates, m. p. 112—113° (Found : C, 88·0; H, 6·3. $C_{21}H_{18}O$ requires C, 88·1; H, 6·3%). Its alcoholic solution showed an intense blue fluorescence in daylight.

In one experiment a colourless compound, presumably the *photo-oxide*, was also isolated (cf. Sandin and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 3098). It formed colourless needles from alcohol, m. p. 210—212° (after sintering) (Found : C, 79·25; H, 5·45. $C_{21}H_{18}O_3$ requires C, 79·3; H, 5·7%).

2-(2′-*Methoxynaphthoyl*-1′)-*benzoic acid*.—β-Methoxynaphthalene (7·5 g.), phthalic anhydride (8·0 g.), and nitrobenzene (100 c.c.) were cooled in ice and treated with aluminium chloride (12·5 g.) during 1 hour, with stirring. After 3 hours, the solution was kept at room temperature, with shaking, for 70 hours. After decomposition in the usual way, the acid was obtained; it crystallised from toluene as yellow prisms (4·5 g.), m. p. 191—194°. Its constitution was proved by demethylation with aluminium chloride in boiling benzene, followed by conversion into the lactone, m. p. 195—196° (Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 3546).

The same hydroxy-acid was obtained, in poor yield, following a similar experiment with β-naphthol.

Action of Sulphuric Acid on 2-(2′-*Hydroxynaphthoyl*-1′)-*benzoic Acid Lactone*.—A solution of the lactone (1 g.) in concentrated sulphuric acid (10 c.c.) was heated at 60—70° for 6 hours, and then poured on ice. The solid obtained was dissolved in aqueous alcohol, from which phthaloylnaphthol, m. p. 196—197° (alone, or mixed with an authentic specimen) (0·06 g.), was obtained. The alcoholic liquors, on evaporation, deposited phthalic acid (0·26 g.), m. p. 196° (Found : C, 57·6; H, 3·7. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%), converted into phthalic anhydride, m. p. 128—130°, by sublimation. Phthalic acid was also obtained following a similar experiment with the free acid. Both the free acid and the lactone gave cherry-red solutions in sulphuric acid.

2-(2′-*Methoxybenzoyl*)-1-*naphthoic Acid*.—A solution in ether (30 c.c.) and benzene (15 c.c.) of

o-anisylmagnesium bromide (from 25 g. of *o*-bromoanisole) was added slowly to a boiling solution of 1 : 2-naphthalic anhydride (26·4 g.) in anhydrous benzene (200 c.c.). The thick yellow precipitate was filtered off and decomposed with ice and dilute sulphuric acid in the presence of ether. The ether solution was extracted with sodium carbonate, and the *acid* prepcipitated (20 g.). After purification through the acetoxy-lactone, it formed colourless transparent prisms, m. p. 185—187° (Found: C, 74·45; H, 4·6. $C_{19}H_{14}O_4$ requires C, 74·45; H, 4·6%). The *acetoxy-lactone*, prepared by heating the acid (20 g.) with acetic anhydride (40 c.c.) and pyridine (130 c.c.) on the steam-bath for 2 hours, formed colourless transparent prisms, from toluene, m. p. 209—211° (Found: C, 72·9; H, 4·7. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%). Attempts to ring-close the acid with sulphuric acid, or with benzoyl chloride and a trace of sulphuric acid, were unsuccessful.

The author thanks Professor J. W. Cook, F.R.S., for his interest in this work, which has been made possible by the award of an Imperial Chemical Industries Research Fellowship. All analyses are microanalyses by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, October 7th*, 1946.]

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177. *New Potential Chemotherapeutic Agents. Part VII. Experiments on the Synthesis of 8-Aminopurines.*

By F. E. KING and T. J. KING.

With the possibility that the synthesis of potential adenine inhibitors might lead to a plasmodicidal compound, the preparation of basically-substituted purines related to adenine, *e.g.* (II; R = NH·$[CH_2]_3$·NEt_2), has been investigated. The principal intermediates obtained in this research are the previously unknown purines (V; R = NHPh) and (VI; R = OH), and the triazole (IX; R = Me), but only in (VI; R = OH), the methylthio-group of which does not react with amines, was it possible to replace the 6-hydroxyl group by a basic substituent. The arylcarbamides (IV; R = SH) and (IV; R = NH_2) were resistant to cyclisation, but the derivative (IV; R = OH) was successfully converted into (V; R = NHPh), which was also directly obtained from the hydrochloride of (III) and phenylcyanamide in boiling butanol, possibly through the *O*-butyl ether (IV; R = O·C_4H_9).

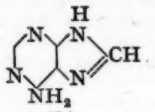
IN its application to antimalarial compounds, the current theory as to the mode of action of the more specific chemotherapeutic agents was first expressed by Oesterlin (*Klin. Woch.*, 1936, **15**, 1719), who suggested that the activity of mepacrine and pamaquin arose from their easy reduction to dihydro-derivatives, a property which enabled them to inhibit some riboflavin-containing enzyme essential to the metabolism of the parasite. The close structural resemblance of these drugs to riboflavin is in agreement with this idea, and the ability, not only of mepacrine but also of some of the newer pyrimidine antimalarials (see Curd and Rose, *J.*, 1946, 343 *et seq.*), to function as riboflavin antagonists has recently been experimentally demonstrated in nutritional investigations with *Lactobacillus casei* by Madinaveitia (*Biochem. J.*, 1946, **40**, 373).

If, as these observations seem to imply, antimalarial action is dependent on the inhibition of well-known enzymes, it should also be possible, by means of suitably constituted reagents, to arrest the growth of the plasmodia by interfering with the synthesis or utilisation of other co-enzyme constituents, for example, the purines adenine and guanine. Such a hypothesis has, in fact, lately been propounded by Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1946, 360) to account for the antimalarial properties of certain 5-methylpyrimidines, which these authors consider may be due to blocking of the purine biosynthesis by the 5-substituent. From considerations similar to those advanced by Todd and his colleagues (*loc. cit.*), it occurred to us that useful results might follow from the preparation of purine bases as potential antimalarial agents, and we were for a time engaged in the synthesis of appropriately substituted compounds related to adenine (I).

The derivatives of (I) considered most likely to possess biological activity were those incorporating the characteristic dialkylaminoalkylamino- side chain and the chlorinated or methoxylated aniline residue typical of what may be termed the riboflavin antimalarials. Of the several possible arrangements of these presumably essential components about the adenine, or somewhat more readily obtainable 2-methyladenine, nucleus, that shown as (II; R = NH·$[CH_2]_3$·NEt_2) was selected as the first objective. Although the project has made some progress, its full development has been hindered by unexpected difficulties, the nature of which is indicated in the following account of the experiments.

With 4 : 5-diamino-6-hydroxy-2-methylpyrimidine (III) as the starting point, the sequence of reactions in the proposed synthesis of (II; R = NH·$[CH_2]_3$·NEt_2) was (i) formation of the 5-*p*-chlorophenylthiocarbamido-derivative; (ii) its cyclisation to 8-*p*-chloroanilino-6-hydroxy-2-methylpurine (II; R = OH); (iii) replacement of the 6-hydroxyl group by chlorine, giving

(II; R = Cl); and (iv) substitution of the chlorine by a diethylaminopropylamino-group. Since there was no reason to suppose that the necessary conditions would be appreciably affected by slight variations in structure, the reactions were for the most part investigated with the anilino- rather than the *p*-chloroanilino-derivatives.



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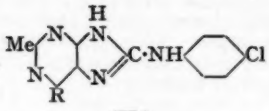

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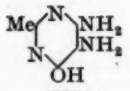

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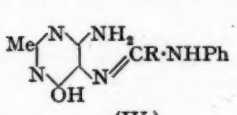

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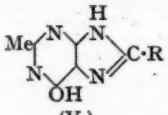
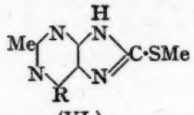


(V.)



(VI.)

The action of ammonium phenyldithiocarbamate on the diaminopyrimidine (III) in aqueous solution at 100° gave the *5-phenylthiocarbamido*-derivative (IV; R = SH), but the latter remained unchanged on attempted ring-closure in boiling water, and with lead hydroxide in refluxing ethanol or *iso*amyl alcohol. Methylation to the potentially more reactive methylthio-compound (IV; R = SMe) could not be accomplished. However, prolonged heating of (IV; R = SH) with pyridine effected cyclisation, but with the elimination of aniline, so that the product was *6-hydroxy-8-mercapto-2-methylpurine* (V; R = SH). The constitution of this compound was confirmed by means of an independent synthesis from the diamine (III) by fusion with thiourea, and also by the formation of *6-hydroxy-8-methylthio-2-methylpurine* (V; R = SMe) on treatment with methyl iodide in aqueous sodium hydroxide. Unfortunately, the methylthio-derivative could not be utilised for the synthesis of the 8-anilinopurine (V; R = NHPh), or even of (V; R = NH·[CH_2]$_3$·NEt_2), since it failed to react with either aniline or γ-diethylaminopropylamine.

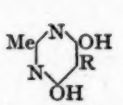
In order to permit of the use of other methods of ring-closure to the required base (V; R = NHPh), the original scheme was modified by substituting as an intermediate *4-amino-5-(N′-phenylcarbamido)-6-hydroxy-2-methylpyrimidine* (IV; R = OH), which was prepared from (III) by the action of phenyl *iso*cyanate in boiling toluene. Treatment of the carbamidopyrimidine with both phosphoryl chloride and phosphorus pentachloride under various conditions did not succeed in giving any purifiable substance, but with phosphorus trichloride in refluxing toluene a product having the composition of the required *8-anilino-6-hydroxy-2-methylpurine* (V; R = NHPh) was obtained. Since there is also a possibility of reaction between the substituents at the 5- and the 6-position, which would result in the formation of 6-amino-8-hydroxy-9-phenyl-2-methylpurine, the synthesis did not provide definite proof of the constitution of the new base. Moreover, the product exhibited an unexpected stability towards chlorinating agents, a property which could be interpreted as a further manifestation of the inertness of the 8-substituent already encountered in the analogous 8-methylthiopurine (V; R = SMe). Accordingly, a method was designed for the synthesis of (V; R = NHPh) which would leave the structure of the final product in no doubt. This involved the preparation of the guanidine (IV; R = NH_2) which was effected by prolonged heating of (III), in the form of its hydrochloride, with phenylcyanamide in refluxing ethanol. The condensation was repeated with p-*chlorophenylcyanamide*, both guanidines being further identified by their *hydrochlorides* and *picrates*, but in no circumstances could the cyclisation of either guanidine be achieved. Nevertheless, the product (V; R = NHPh) was ultimately obtained when attempting to accelerate the reaction of phenylcyanamide with the pyrimidine (III) by using boiling butanol instead of ethanol as solvent. The base gave a dihydrated *hydrochloride* and was in every respect identical with the substance already prepared from (IV; R = OH), the constitution of which is thus established.

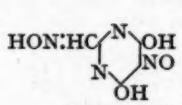
The derivative (IV; R = NH_2) could not be detected in the reaction product, and together with the fact that it failed to cyclise under similar conditions, it is fairly certain that the guanidine is not an intermediate in the cyclisation. It is possible to suggest an explanation for the variation of product with solvent if the likely supposition is made that a preliminary step is the formation from the cyanamide of an imino-ether, Ph·NH·C(:NH)·O-alkyl. Two alternatives are then possible in the subsequent condensation with the pyrimidine 5-amino-group: (i) elimination of alcohol, giving the guanidine (IV; R = NH_2); or (ii) loss of ammonia, a reaction

similar to that introduced by Schmidt (*Ber.*, 1914, **47**, 2548) for the preparation of *N*-substituted imino-ethers, giving (IV; R = O-alkyl). Normally, guanidine formation would be expected to occur, but when O-alkyl is the comparatively inert butoxy-group, formation of the substituted imino-ether (IV; R = O·C_4H_9) would take precedence, the final ring-closure to (V; R = NHPh), a reaction of the amidine type, being facilitated by the favourable spatial configuration of the molecule.

Since the anilinohydroxypurine (V; R = NHPh) was highly resistant to attack by chlorinating agents, further progress in the direction of (II; R = dialkylaminoalkylamino-) was impossible. Shortly afterwards, Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 1271) reported similar difficulties in attempting to convert guanine hydrochloride into 6-chloro-2-aminopurine. These results are surprising, particularly when compared with those from later experiments on the methylthiopurine (V; R = SMe). Under the conditions used by Baddiley and Topham (*J.*, 1944, 678) for the preparation of trichloropyrimidine from barbituric acid, *viz.*, heating with phosphoryl chloride and dimethylaniline, the only isolable product was a small yield of 6-N-*methylanilino*-8-*methylthio*-2-*methylpurine* (V; R = NMePh), but, with phosphoryl chloride alone, no difficulty was experienced in obtaining the 6-*chloro*-8-*methylthio*-2-*methylpurine* (VI; R = Cl). Heating the latter in toluene with γ-diethylaminopropylamine gave the corresponding basically-substituted purine (VI; R = NH·$[CH_2]_3$·NEt_2) which was isolated as the *hydrochloride*. The necessary γ-diethylaminopropylamine was prepared by reduction of β-diethylaminopropionitrile in ammoniacal methanol over Raney nickel, and was characterised by its picrate, *picrolonate*, and *flavianate*.

In connexion with other work on purine analogues, 5-amino-4 : 6-dihydroxy-2-methylpyrimidine (VII; R = NH_2) was required; this we proposed to prepare from 4 : 6-dihydroxy-2-methylpyrimidine (VII; R = H) *via* the 5-nitroso-derivative. Both the nitrosation of (VII;


(VII.)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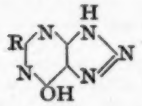
(IX.)

R = H) and its reaction with *p*-chlorobenzenediazonium chloride have been described by Lythgoe, Todd, and Topham (*J.*, 1944, 315) but no attempt was made to isolate the products. On repeating these reactions, 5-p-*chlorobenzeneazo*-4 : 6-*dihydroxy*-2-*methylpyrimidine* (VII; R = N_2·C_6H_4·Cl) was obtained and characterised, but the bright green solid which separated on adding nitrous acid to the pyrimidine (VII; R = H) proved to be a dinitroso-compound, and not the expected derivative (VII; R = NO). In view of the reactivity of the 2-methyl group in certain hydroxypyrimidines, *e.g.*, 4-hydroxy-2-methylpyrimidine, which is oxidised by nitrous acid to 4-hydroxypyrimidine-2-carboxylic acid (Huber and Hölscher, *Ber.*, 1938, **71**, 87), the product appeared to be 5-*nitroso*-4 : 6-*dihydroxy*-2-iso*nitrosomethylpyrimidine* (VIII). The considerably increased yield obtained on using a second equivalent of nitrite supported this view, which was confirmed by reduction of the derivative to the corresponding *diamine*.

From the diaminopyrimidine (III) the triazolopyrimidine (IX; R = Me) was prepared by the action of nitrous acid, and was isolated as a hydrated double *salt*, $C_5H_5ON_5$,$C_5H_4ON_5Na$. As with the purine (V; R = NHPh), attempts to replace the 6-hydroxyl group by chlorine were unsuccessful. Roblin, Lampen, English, Cole, and Vaughan (*J. Amer. Chem. Soc.*, 1945, **67**, 290) subsequently described the antibacterial activity of the lower homologue (IX; R = H), and when tested *in vitro* against *Staph. aureus* by the method of Heatley (*Lancet*, 1941, **2**, 177), the 2-methyltriazole (IX; R = Me) was found to possess comparable activity.

Hydrochlorides of the amine (VI; R = NH·$[CH_2]_3$·NEt_2), and of the guanidine (IV; R = NH_2) and the analogous *p*-chloro-compound were tested against *P. gallinaceum* infections in chicks. The tests were kindly carried out by Miss I. M. Tonkin, National Institute of Medical Research, London, N.W. 3, who reports that none of the compounds has antimalarial activity.

Experimental.

4-*Amino*-5-(*N'-phenylthiocarbamido*)-6-*hydroxy*-2-*methylpyrimidine* (IV; R = SH).—4 : 5-Diamino-6-hydroxy-2-methylpyrimidine monohydrate (Traube, *Annalen*, 1923, **43**, 287) (5 g., 1 mol.) in aqueous sodium hydroxide (1·43 g., 1·13 mol., in 25 c.c.), and a solution of ammonium phenyldithiocarbamate (*Org. Synth.*, **6**, 72) (6·65 g., 1·13 mol.) in water (25 c.c.), were heated on a steam-bath for 6 hours. The precipitate, together with a further quantity of solid obtained by the addition of acid, was collected and purified by dissolving in 2N-sodium hydroxide. The *phenylthiocarbamide* (6·6 g., 76%) obtained on acidifying the filtered solution was crystallised from a large volume of boiling water, and formed

colourless microscopic tablets, m. p. >310° (Found: C, 52·5; H, 5·0; S, 10·8. $C_{12}H_{12}ON_6S$ requires C, 52·4; H, 4·7; S, 11·6%). The compound was insoluble in organic solvents, but dissolved readily in aqueous sodium hydroxide forming a mono-sodium salt and a more soluble di-sodium salt. It was not affected either by heating in boiling water for 48 hours, or on treatment with freshly prepared lead hydroxide in refluxing ethanol or *iso*amyl alcohol for 24 hours.

6-*Hydroxy*-8-*mercapto*-2-*methylpurine* (V; R = SH).—(*a*) The phenylthiocarbamide (IV; R = SH) (5 g.) was heated in boiling pyridine (50 c.c.) for 36 hours, and the solid collected and dissolved in 2N-sodium hydroxide. The micro-crystalline pale fawn powder obtained on acidification passed through filter paper, even after heating to 100°, and the product was accordingly isolated by centrifugation, and washed with water and ethanol. The resulting 6-*hydroxy*-8-*mercapto*-2-*methylpurine*, a light brown powder (2·7 g., 81%), m. p. >310°, which was very sparingly soluble in water and organic solvents, was purified by precipitation from its aqueous alkaline solution with acid (Found: C, 39·4; H, 3·7; S, 17·4. $C_6H_4ON_4S$ requires C, 39·5; H, 3·3; S, 17·6%). It gave both a mono- and a di-sodium salt, the former being sparingly soluble.

(*b*) When 4 : 5-diamino-6-hydroxy-2-methylpyrimidine (5 g.) and excess of thiourea (10 g.) were fused over a flame for 30 minutes, the mixture frothed and evolved ammonia. After cooling, the mercaptopurine was extracted with dilute alkali, the purified product (4·95 g., 86%) being identical in appearance, solubilities, etc., with that from reaction (*a*) (Found: S, 17·0%).

6-*Hydroxy*-8-*methylthio*-2-*methylpurine* (V; R = SMe).—6-Hydroxy-8-mercapto-2-methylpurine (5 g.) in excess of 2N-sodium hydroxide was shaken at room temperature with methyl iodide (4·0 g., 1·1 mol.) for 20 minutes. On neutralisation, the *methylthiopurine* (4·3 g., 81%) separated in pale fawn needles, m. p. >310°. The methyl ether is more soluble than the parent compound (V; R = SH), dissolving in both acids and alkalis and crystallising well from water (Found: C, 42·7; H, 4·4; N, 28·8; S, 16·4. $C_7H_6ON_4S$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%).

On heating with aniline or γ-diethylaminopropylamine the methylthiopurine was either largely unchanged or, under extreme conditions, suffered decomposition.

4-*Amino*-5-(N′-*phenylcarbamido*)-6-*hydroxy*-2-*methylpyrimidine* (IV; R = OH).—4 : 5-Diamino-6-hydroxy-2-methylpyrimidine (7 g., 1 mol.), dried at 140°/0·6 mm. over phosphoric oxide, was heated with phenyl *iso*cyanate (7 g., 1·17 mol.) in boiling toluene (100 c.c.) for 8 hours. The colourless solid product (11·5 g., 88·8%), which was very sparingly soluble in organic solvents, water, and acids, but readily soluble in alkalis, was crystallised from a large volume of boiling water. The pure *phenylcarbamidopyrimidine* formed colourless microscopic rhombs, m. p. >305° (Found: C, 55·2; H, 5·0; N, 26·5. $C_{12}H_{13}O_2N_5$ requires C, 55·6; H, 5·0; N, 27·0%).

Heating the derivative (2 g.) with phosphoryl chloride (10 c.c.), followed by removal of halide under reduced pressure, dissolution of the residue in ethanol, and precipitation with water, gave an uncrystallisable solid (1·2 g.) devoid of halogen. Prolonged treatment with phosphoryl chloride or phosphorus pentachloride in toluene gave inseparable mixtures of partly chlorinated products.

8-*Anilino*-6-*hydroxy*-2-*methylpurine* (V; R = NHPh).—(*a*) 4-Amino-5-(N′-phenylcarbamido)-6-hydroxy-2-methylpyrimidine (5 g.) in toluene (100 c.c.) was treated with phosphorus trichloride (1·8 g., 2 mol.), and the mixture refluxed for 10 hours. The solid was collected and purified by precipitation from its aqueous solution by addition of a large excess of concentrated hydrochloric acid. The purine (V; R = NHPh) was thus obtained as a sparingly soluble *hydrochloride* (4·6 g., 80·4%), crystallising in minute pale cream-coloured plates, m. p. >310° (Found: C, 46·2; H, 5·3; Cl, 12·0. $C_{12}H_{11}ON_5,HCl,2H_2O$ requires C, 46·0; H, 5·1; Cl, 11·3%. Found, after drying at 100°: C, 50·0; H, 4·9. $C_{12}H_{11}ON_5,HCl,\frac{1}{2}H_2O$ requires C, 50·2; H, 4·5%).

(*b*) 4 : 5-Diamino-6-hydroxy-2-methylpyrimidine hydrochloride (5 g.) and phenylcyanamide were refluxed in dry *n*-butanol for 25 hours. The cooled product was filtered, thus giving a fawn solid (6 g.), which was extracted with hot water (300 c.c.). The undissolved halogen-free product (2·3 g., 33·5%) was soluble in alkalis and sparingly soluble in organic solvents. It was purified by adding a large excess of hydrochloric acid to its alkaline solution; the hydrochloride, m. p. >310°, then separated in minute almost colourless plates (Found: C, 45·7; H, 5·1; N, 22·2; Cl, 11·1%. Found after drying at 100°: C, 50·0; H, 4·5%).

Evaporation of the solution from the hot water extraction gave only unchanged diaminopyrimidine hydrochloride. Yields from the above condensation varied considerably and were sometimes extremely small. Several attempts were made to obtain the 6-chloro-derivative from the purine (V; R = NHPh) using phosphorus chlorides, but only resinous products were obtained.

4-*Amino*-5-(N′-*phenylguanidino*)-6-*hydroxy*-2-*methylpyrimidine* (IV; R = NH_2).—Finely divided 4 : 5-diamino-6-hydroxy-2-methylpyrimidine hydrochloride (1·5 g.) and excess of phenylcyanamide (2 g.) were heated in boiling ethanol (60 c.c.) for 30 hours. The resulting solid (2·2 g., 83%) was collected and the guanidine purified as *hydrochloride* by crystallisation from dilute hydrochloric acid, from which the salt separated as small colourless plates, m. p. 295° (decomp.), soluble in alkali, very sparingly soluble in organic solvents (Found: C, 45·5; H, 5·5; N, 26·5; Cl, 11·6. $C_{12}H_{14}ON_6,HCl,H_2O$ requires C, 46·1; H, 5·4; N, 26·8; Cl, 11·4%. Found after drying at 100°: C, 47·2; H, 5·3. $C_{12}H_{14}ON_6,HCl,\frac{1}{2}H_2O$ requires C, 47·4; H, 5·3%).

On treating a solution of the pure hydrochloride with aqueous sodium picrate, the very sparingly soluble *picrate* separated as thick, minute yellow prisms, m. p. 270° (decomp.) (Found: C, 42·8; H, 3·9. $C_{12}H_{14}ON_6,C_6H_3O_7N_3,H_2O$ requires C, 42·7; H, 3·8%. Found after drying at 100°: C, 43·8; H, 3·9. $C_{12}H_{14}ON_6,C_6H_3O_7N_3$ requires C, 44·3; H, 3·5%).

Attempted ring-closure to (V; R = NHPh) by heating alone, or in high boiling solvents, or with concentrated hydrochloric acid, was unsuccessful.

p-*Chlorophenylcyanamide*.—To *p*-chlorophenylthiourea (Stolle, *J. pr. Chem.*, 1932, **134**, 282) (18·5 g., 1 mol.) and lead acetate (50 g., 1·5 mol.) in water (200 c.c.) at 90° a solution of potassium hydroxide (25 g., 4 mol.) in water (50 c.c.) was added. The mixture was shaken during 15 minutes' heating on a steam-bath, and, after removal of lead sulphide, the clear solution was cooled and acidified with acetic acid. p-*Chlorophenylcyanamide* separated as a colourless solid (9·4 g., 61%), insoluble in water, very

soluble in the common organic solvents, and crystallising from aqueous ethanol in long silky colourless needles, m. p. 107° (Found: C, 55·0; H, 3·2; Cl, 24·1. $C_7H_5N_2Cl$ requires C, 55·0; H, 3·3; Cl, 23·3%).

4-Amino-5-(N'-p-chlorophenylguanidino)-6-hydroxy-2-methylpyrimidine.—Finely powdered 4 : 5-diamino-6-hydroxy-2-methylpyrimidine hydrochloride (5 g.) and excess of *p*-chlorophenylcyanamide (10 g.) were refluxed in ethanol for 30 hours. The crystalline guanidine was collected and purified as the *dihydrochloride* by precipitation from an alkaline solution with hydrochloric acid. The salt formed a colourless microcrystalline powder, m. p. 302° (decomp.), virtually insoluble in organic solvents (Found: C, 39·4; H, 4·1; Cl, 29·4. $C_{12}H_{13}ON_6Cl,2HCl$ requires C, 39·4; H, 4·1; Cl, 29·8%).

The *picrate*, which was precipitated from aqueous solutions of the hydrochloride and sodium picrate, crystallised from ethanol in minute yellow prisms, m. p. 268° (decomp.) (Found: C, 39·9; H, 3·6; N, 23·6. $C_{12}H_{13}ON_6Cl,C_6H_3O_7N_3,H_2O$ requires C, 40·2; H, 3·3; N, 23·4%).

6-N-Methylanilino-8-methylthio-2-methylpurine (VI; R = NMePh).—6-Hydroxy-8-methylthio-2-methylpurine (3 g.) was refluxed for 3 hours with phosphoryl chloride (3·2 c.c.) and dimethylaniline (2 c.c.). The dark liquid was poured on ice, and after 1 hour the water layer was decanted and the residual tarry product triturated with a little ethanol. The crystalline residue (0·9 g., 22%) was the 6-methylanilinopurine *hydrochloride*, which separated from alcohol–ether as a grey microcrystalline powder, m. p. 270—271° (decomp.), soluble in water, ethanol, and acetone, insoluble in ether (Found: C, 52·5; H, 6·2; Cl, 10·4. $C_{14}H_{15}N_5S,HCl,C_2H_6O$ requires C, 52·2; H, 6·0; Cl, 9·7%).

6-Chloro-8-methylthio-2-methylpurine (VI; R = Cl).—6-Hydroxy-8-methylthio-2-methylpurine (3 g.) was refluxed for 3 hours with excess of phosphoryl chloride. The thick black syrup remaining after evaporation was treated with sodium carbonate (2 g.), water (*ca.* ½ c.c.), and toluene (50 c.c.), and the mixture heated to boiling. The hot toluene solution was decanted, and on cooling it deposited the *chloropurine* (1·75 g., 53%) in long colourless silky needles. The product was easily soluble in ethanol and almost insoluble in water. Crystallised from toluene, the pure compound had m. p. 231° (Found: C, 39·8; H, 3·5; Cl, 16·9. $C_7H_7N_4ClS$ requires C, 39·2; H, 3·3; Cl, 16·6%).

γ-Diethylaminopropylamine (cf. Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725).—Reduction of β-diethylaminopropionitrile (Holcomb and Hamilton, *ibid.*, 1942, **64**, 1309) (15 g.) in ammoniacal methanol (150 c.c. saturated at 0°) at 100°/100 atm. for 20 minutes gave γ-diethylaminopropylamine (12·3 g., 82%), b. p. 175°. It was identified by the picrate, m. p. 192° (decomp.) (literature 194°); the *picrolonate*, m. p. 261° (decomp.), a microcrystalline powder, very sparingly soluble in hot alcohol (Found: C, 49·4; H, 5·4. $C_7H_{18}N_2,2C_{10}H_8O_5N_4$ requires C, 49·2; H, 5·4%); and the *flavianate*, yellow-orange, felted needles, m. p. 260° (decomp.), readily soluble in hot ethanol (Found: C, 45·8; H, 5·3. $C_7H_{18}N_2,C_{10}H_6O_8N_2S$ requires C, 46·0; H, 5·4%).

6-γ-Diethylaminopropylamino-8-methylthio-2-methylpurine (VI; R = NH·[CH_2]$_3$·NEt_2).—The hydroxypurine (VI; R = OH) (5 g.) was chlorinated as before, and the product remaining after removing excess of phosphoryl chloride was heated with γ-diethylaminopropylamine (5 g., 1·5 mol.) in boiling toluene (75 c.c.) for 10 hours. The solvent was evaporated under reduced pressure and the tarry residue extracted with ethanol (150 c.c.). Dry hydrogen chloride was passed into the extract and the volume reduced to 50 c.c. on a steam-bath. On cooling, the purine *hydrochloride* (14·5 g., 80%) separated as brown tablets, soluble in water, alcohol, and acetone; when recrystallised from ethanol–ether it formed colourless prisms, m. p. 243° (Found: C, 44·0; H, 6·9; N, 22·1; Cl, 19·2; S, 8·0. $C_{14}H_{24}N_6S,2HCl$ requires C, 44·1; H, 6·8; N, 22·1; Cl, 18·6; S, 8·4%).

On treating the above alcoholic extract with picric acid, the sparingly soluble *picrate* was obtained, which crystallised from alcohol as a monohydrate in yellow needles, m. p. 110° (decomp.) (Found: C, 40·3; H, 4·3; N, 21·0. $C_{14}H_{24}N_6S,2C_6H_3O_7N_3,H_2O$ requires C, 39·8; H, 4·1; N, 21·4%).

5-p-Chlorobenzeneazo-4 : 6-dihydroxy-2-methylpyrimidine (VII; R = N_2·C_6H_4·Cl) (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—A solution of *p*-chlorobenzenediazonium chloride, from *p*-chloroaniline (25 g.), in excess of hydrochloric acid was slowly added to 4 : 6-dihydroxy-2-methylpyrimidine (25 g.) in 2N-sodium carbonate (100 c.c.) containing excess of sodium acetate. The precipitated pale yellow solid (39·9 g., 76%) was collected and dried at 100°. The *pyrimidine* was sparingly soluble in organic solvents, but was crystallised from a large volume of ethanol, forming yellow needles, m. p. >310°, which dissolved in alkali to an orange solution (Found: C, 50·0; H, 3·5. $C_{11}H_9O_2N_4Cl$ requires C, 49·9; H, 3·4%).

5-Nitroso-4 : 6-dihydroxy-2-isonitrosomethylpyrimidine (VIII) (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—Sodium nitrite (5·5 g., 2 mol.) was added to the pyrimidine (VII; R = H) (5 g., 1 mol.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) dissolved in 2N-sodium hydroxide, and the mixture treated with excess of hydrochloric acid. A dark green solid immediately separated, which was collected and washed with alcohol and ether. The *dinitrosopyrimidine* (6·4 g., 89%) became grey at 100° but did not melt below 310° (Found: C, 32·2; H, 2·5. $C_5H_4O_4N_4$ requires C, 32·6; H, 2·2%). It was insoluble in organic solvents, but dissolved in aqueous alkali from which it was precipitated by acid. Repeated dissolution in alkali destroyed the characteristic green colour, and the pyrimidine was better purified through the *sodium* salt. This separated on the addition of alcohol to its aqueous solution as a bright green microcrystalline powder, m. p. >310°, containing water of crystallisation (Found: C, 21·5; H, 2·6; N, 19·9. $C_5H_2O_4N_4Na_2,2\frac{1}{2}H_2O$ requires C, 22·0; H, 2·6; N, 20·5%. Found after drying at 100°: C, 24·1; H, 1·4. $C_5H_2O_4N_4Na_2,H_2O$ requires C, 24·4; H, 1·6%).

5-Amino-4 : 6-dihydroxy-2-aminomethylpyrimidine.—The nitroso-compound (VIII) (11·5 g.) was added to aqueous ammonia (50 c.c. of 17%) saturated with hydrogen sulphide at 0°. After a few seconds the green colour disappeared, and a yellow solid was deposited, probably an ammonium salt. This was dissolved in hot water, and on acidifying with concentrated hydrochloric acid the diamine *hydrochloride* separated as a light pink powder (6·1 g., 42·6%), with decomposition point 200° (Found: C, 26·3; H, 4·8. $C_5H_8O_2N_4,2HCl$ requires C, 26·2; H, 4·4%).

Both the hydrochloride and the free base are very soluble in water, sparingly soluble in organic solvents. Heating the base with water led to decomposition with elimination of ammonia.

5 : 6-(4 : 5-Triazolo)-4-hydroxy-2-methylpyrimidine (IX; R = Me).—The diaminopyrimidine (III) (5 g.), dissolved in excess of hydrochloric acid, was treated at 0° with aqueous sodium nitrite (2·2 g. in 10 c.c.), and after 10 minutes the solution was carefully neutralised with solid sodium hydrogen carbonate.

The precipitated solid (3 g., 50%) crystallised from water in long plates, m. p. 310°, soluble in aqueous alkali and acid, and was found on analysis to consist of the triazolopyrimidine acid sodium salt *trihydrate* (Found: C, 31·4; H, 4·3; N, 37·0; Na, 6·1. $C_5H_5ON_5,C_5H_4ON_5Na,3H_2O$ requires C, 31·7; H, 4·0; N, 37·0; Na, 6·1%). The compound was remarkably resistant to chlorinating agents, being almost quantitatively recovered even after fusion with phosphorus pentachloride.

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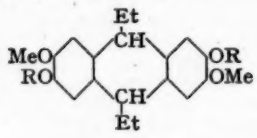
178. *The Constituents of Natural Phenolic Resins. Part XXI.* The Structure of Diisoeugenol.*

By NEVILLE J. CARTWRIGHT and ROBERT D. HAWORTH.

Structure (I; R = H) suggested for di*iso*eugenol in 1931 has been disproved by the synthesis of a tetramethoxyanthracene derivative of structure (I; R = Me) which, in its ready dehydrogenation, differs markedly from di*iso*eugenol dimethyl ether. Structure (III; R = H) is rejected because (*a*) such a lignan structure would be inconsistent with the difficulties experienced in the dehydrogenation of di*iso*eugenol derivatives, and (*b*) synthetic analogues of (III; R = Me) give colour reactions which differ from those shown by di*iso*eugenol dimethyl ether. Structure (IV; R = H) recently advanced by Müller *et al.* is regarded as the most likely structure for di*iso*eugenol for the following reasons. The ketone (VIII) has been synthesised and shown to be identical with the red oxidation product of di*iso*eugenol dimethyl ether which Haworth and Mavin (*J.*, 1931, 1363) had regarded as an anthrone derivative. The hydrindenes (IX) and (IV; R = Me) have been synthesised; both resist dehydrogenation and both give colour reactions resembling those exhibited by di*iso*eugenol dimethyl ether. The hydrindene (IV; R = Me) is, however, not identical with di*iso*eugenol dimethyl ether, but the difference may be stereochemical.

THE constitution of di*iso*eugenol has recently been the subject of eight communications by Müller *et al.* [(i) *Ber.*, 1942, **75**, 692; (ii) *ibid.*, p. 891; (iii) *ibid.*, 1943, **76**, 855; (iv) *ibid.*, p. 1061; (v) *ibid.*, p. 1119; (vi) *ibid.*, 1944, **77**, 6; (vii) *ibid.*, p. 12; (viii) *ibid.*, p. 159] and as conclusions similar to our present views have been reached, it is desirable, in spite of the incomplete nature of our work, to place on record our contributions to this problem.

In 1931, Haworth and Mavin (*J.*, 1931, 1363) suggested that di*iso*eugenol had structure (I; R = H) instead of the *cyclo*butane structure (II) proposed by earlier workers. The introduction of this anthracene structure rested very largely on the isolation of 2 : 3 : 6 : 7-tetramethoxyanthraquinone from the products of the chromic acid oxidation of di*iso*eugenol dimethyl ether, but Szeki (*Annalen*, 1933, **507**, 197) and Szeki and Haraszti (*ibid.*, **508**, 294), disregarding



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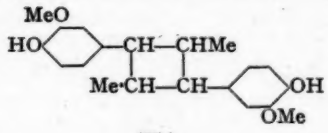

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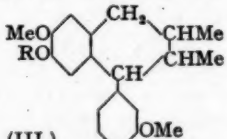


(III.)

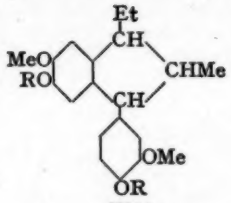
this evidence, adhered to the *cyclo*butane structure (II). Müller *et al.* [(i) and (ii)] first proposed the lignan structure † (III; R = H) but in later communications they abandoned this in favour of the hydrindene structure (IV; R = H) which resembles the metanethole structure suggested by Baker and Enderby (*J.*, 1940, 1094).

Müller's conclusions depend to a great extent upon the oxidation to *o*-veratroylveratric acid and upon the interpretation of the properties of a hydroxy-ketone obtained as one of the products of oxidation of di*iso*eugenol dimethyl ether. This substance, formulated as (V) in his later papers, is readily converted into a red anhydro-derivative, which is now regarded as an indene derivative, but for which Haworth and Mavin (*loc. cit.*) had tentatively proposed an anthrone structure. In our opinion Müller's work is inconclusive; the following observations made over a period of years, although equally inconclusive, have led us quite independently to the view that di*iso*eugenol is best represented by the hydrindene structure (IV; R = H).

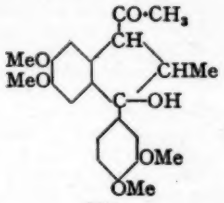
* The last communication (*J.*, 1944, 535) of this series was erroneously numbered as Part XIX instead of Part XX.

† Oliverio (*Gazzetta*, 1943, **73**, 270) reports that he suggested the lignan formula (III; R = H) for di*iso*eugenol in 1937.

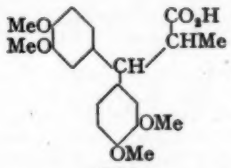
In 1937, unpublished work with Miss W. Robson, B.Sc., showed that di*iso*eugenol dimethyl ether resembled 2 : 3 : 6 : 7-tetramethoxy-9 : 10-dihydroanthracene in absorption spectra, both



(IV.)



(V.)



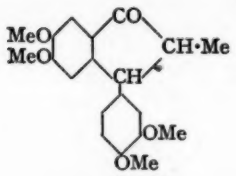
(VI.)

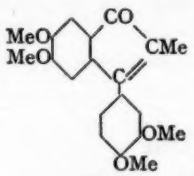
showing maximum absorption at a wave-length of 2850 A., but structural similarity cannot be inferred, as the veratrole nucleii present in both structures are responsible for the absorption. At this stage, unsuccessful attempts were made to dehydrogenate di*iso*eugenol dimethyl ether with lead tetra-acetate, palladium black, and selenium and aluminium chloride, and numerous later efforts have been equally unsuccessful. The dihydroanthracene structure (I) can now be discarded, because Müller's observation that an anthracene derivative, and not a dihydroanthracene, is obtained by the condensation of veratrole and propaldehyde, indicates that dihydroanthracenes are characterised by an instability which is not shown by di*iso*eugenol dimethyl ether. In addition, we have reduced the highly fluorescent 2 : 3 : 6 : 7-tetramethoxy-9 : 10-diethylanthracene by means of sodium and amyl alcohol to 2 : 3 : 6 : 7-*tetramethoxy*-9 : 10-*diethyl*-9 : 10-*dihydroanthracene* (I; R = Me), m. p. 148°. Unlike di*iso*eugenol dimethyl ether, this was readily dehydrogenated with lead tetra-acetate in glacial acetic acid solution to the corresponding anthracene derivative, and when a drop of concentrated nitric acid was added to its acetic acid solution a red coloration with a permanent blue reflex was obtained which differed from the cherry-red test given by di*iso*eugenol dimethyl ether.

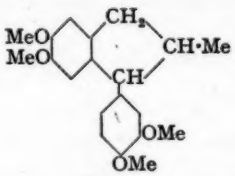
Our failures, mentioned above, to dehydrogenate di*iso*eugenol dimethyl ether are equally inconsistent with the 1-phenyl-1 : 2 : 3 : 4-tetrahydronaphthalene structure (III); the expected product, dehydroguaiaretic acid dimethyl ether, is sparingly soluble in alcohol or acetic acid, and its isolation from complex selenium dehydrogenation mixtures has previously (*J.*, 1938, 1681) been accomplished without difficulty. Attempts to synthesise the structure (III; R = Me) by the action of methyl-alcoholic hydrogen chloride, glacial acetic, and hydrochloric acid mixtures, 100% formic acid, sulphuric acid of various strengths, acetic and sulphuric acid mixture, or phosphoric oxide in toluene on guaiaretic acid dimethyl ether, have yielded unchanged materials, frequently in high yield but sometimes contaminated with intractable oils. Other routes investigated included: (*a*) the conversion of *iso*lariciresinol dimethyl ether (*J.*, 1937, 386) into the corresponding 2 : 3-bischloromethyl derivative for subsequent reduction; (*b*) dehydration and reduction of 4-hydroxy-6 : 7-dimethoxy-1-veratryl-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (*J.*, 1938, 1681); (*c*) reduction of 6 : 7-dimethoxy-1-veratryl-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid (*J.*, 1938, 811) and the isomeric 2-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-3-carboxylic acid (*loc. cit.*). These experiments gave either unchanged material or unrecognisable oils, and although these oils may contain diastereoisomeric forms of the structure (III; R = Me), it is unlikely that they contain the highly crystalline di*iso*eugenol dimethyl ether. In addition, 6 : 7-*dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, synthesised from veratrole and ethyl β-hydroxymethylenepropionate, gave colour reactions differing markedly from those of di*iso*eugenol dimethyl ether, and it was smoothly dehydrogenated by lead tetra-acetate to 6 : 7-dimethoxy-1-veratrylnaphthalene, m. p. 160° (*J.*, 1935, 636).

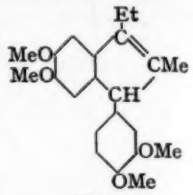
These experiments led us to reject the dihydroanthracene and tetrahydronaphthalene structures (I) and (III), respectively, in favour of the hydrindene structure (IV), and synthetical confirmation of the latter has been sought. Condensation of veratrole and ethyl α-hydroxymethylenepropionate yielded ββ-*diveratryl*-α-*methylpropionic acid* (VI), m. p. 175°, and the corresponding acid chloride was converted into 5 : 6-*dimethoxy*-3-*veratryl*-2-*methylhydrindone* (VII), m. p. 116°. This cyclic ketone was dehydrogenated by heating with palladium at 250° to 5 : 6-*dimethoxy*-3-*veratryl*-2-*methyl*-1-*indone* (VIII), m. p. 194—195°, identical with the orange-red ketone which Haworth and Mavin (*loc. cit.*) previously regarded as 2 : 3 : 6 : 7-tetramethoxy-9-ethylanthrone. The ketone (VII) was readily reduced by Clemmensen's method to give 5 : 6-*dimethoxy*-3-*veratryl*-2-*methylhydrindene* (IX), m. p. 117°. The ketone (VII) also reacted smoothly with ethylmagnesium iodide to yield the oily *indene* derivative (X), which combined

with excess Grignard reagent with the formation of a precipitate and the evolution of ethane. This reaction supports the indene structure (X) and excludes an alternative 1 : 3-dimethyldi-


(VII.)


(VIII.)

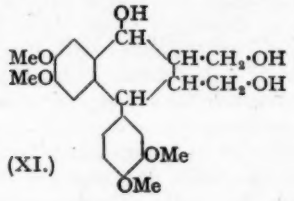

(IX.)

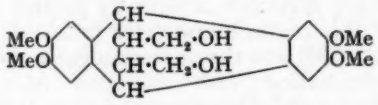

(X.)

hydronaphthalene formula arising from pinacolic change from the intermediate carbinol. The indene derivative (X) was reduced in acetic acid with a very active platinic oxide catalyst to give **5 : 6-*dimethoxy*-3-*veratryl*-2-*methyl*-1-*ethylhydrindene*** (IV; R = Me), m. p. 105°, depressed to 95—98° by admixture with a specimen of di*iso*eugenol dimethyl ether, m. p. 105°. The hydrindene (IV; R = Me), like (IX) and di*iso*eugenol dimethyl ether, resisted dehydrogenation and gave a permanent cherry-red colour with a transient purple reflex when a drop of concentrated nitric acid was added to its solution in glacial acetic acid.

Structure (IV) permits of four racemic modifications. Ciamician and Silber (*Atti R. Accad. Lincei*, 1909, **18**, 1216) converted the readily accessible form of di*iso*eugenol dimethyl ether, m. p. 105°, into an isomer, m. p. 96°, by the action of iodine, and Müller *et al.* (*loc. cit.*) have obtained a third isomer, m. p. 100°, by more indirect methods. These isomeric forms were not available for comparison purposes but the synthetic hydrindene derivative (IV; R = Me), m. p. 105°, is possibly an isomeric modification of di*iso*eugenol dimethyl ether, although efforts to convert it into a diastereoisomeric form by the action of methyl-alcoholic hydrogen chloride have failed.

The oxidation of di*iso*eugenol dimethyl ether to 2 : 3 : 6 : 7-tetramethoxyanthraquinone is in no way inconsistent with the hydrindene structure (IV; R = Me). Dreyfuss (*Gazzetta*, 1936, **66**, 96) has shown that this anthraquinone, together with *o*-veratroylveratric acid and the lactone of 3 : 3′ : 4 : 4′-tetramethoxybenzhydrol-6-carboxylic acid, is obtained by the oxidation of *iso*olivil dimethyl ether (XI). Structure (XII) is postulated as a possible intermediate stage in the conversion into the anthraquinone, and a similar mechanism could obviously be formulated for the oxidation of the hydrindene (IV; R = Me).


(XI.)


(XII.)

Experimental.

2 : 3 : 6 : 7-*Tetramethoxy*-9 : 10-*diethyl*-9 : 10-*dihydroanthracene* (I; R = Me).—2 : 3 : 6 : 7-Tetramethoxy-9 : 10-diethylanthracene (0·3 g.) (Müller, *loc. cit.*, ii) in boiling amyl alcohol (25 c.c.) was treated with sodium (2 g.). After ½ hour's refluxing, water was added, the amyl alcohol was separated and dried, and the solvent removed under reduced pressure. Ethyl alcohol was added to the residue, and the unreduced anthracene derivative (0·15 g.) was collected and the filtrate concentrated; the 9 : 10-dihydroanthracene (I; R = Me) crystallised from methyl alcohol in colourless, dense prisms (0·06 g.), m. p. 147—148° (Found: C, 73·7; H, 7·9; OMe, 34·5. $C_{22}H_{28}O_4$ requires C, 74·1; H, 7·7; OMe, 34·8%), which gave the colour reaction described on p. 949.

Diacetyl Derivatives of Guaiaretic and Dihydroguaiaretic Acids.—Crude extract (5 g.) of guaiacum resin, fused sodium acetate (5 g.), and acetic anhydride (15 c.c.) were heated on the water-bath for 2 hours. Water was added, and the product was collected and fractionally crystallised from ethyl alcohol. *Diacetyl dihydroguaiaretic acid* separated from alcohol in stout irregular prisms, m. p. 112° (Found: C, 69·5; H, 7·1. $C_{24}H_{30}O_6$ requires C, 69·6; H, 7·3%), which gave no colouration with concentrated sulphuric acid. *Diacetyl guaiaretic acid* separated from a small bulk of alcohol in slender hexagonal prisms, m. p. 86—87° (Found: C, 69·2; H, 6·8. $C_{24}H_{28}O_6$ requires C, 69·8; H, 6·8%), which gave a deep red colour with concentrated sulphuric acid and absorbed the theoretical amount of hydrogen.

6 : 7-*Dimethoxy*-1-*veratryl*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-3-*carboxylic Acid.*—The conversion of the lactone of β-veratroyl-α-veratrylidene-*n*-butyric acid into methyl 6 : 7-dimethoxy-1-veratryl-2-methylnaphthalene-3-carboxylate (*J.*, 1938, 811) was best effected with methyl-alcoholic hydrogen chloride, saturated at 0°, and the methyl ester has m. p. 198° and not 178° as previously reported. The corresponding acid was reduced in faintly alkaline solution by boiling for 4 hours with 4% sodium amalgam (150 parts), during which time a stream of carbon dioxide was passed through the solution.

Acidification gave **6 : 7-*dimethoxy*-1-*veratryl*-2-*methyl*-1 : 2-*dihydronaphthalene*-3-*carboxylic acid***, which crystallised from methyl alcohol in clusters of fine needles, m. p. 178—179° (Found : C, 68·4; H, 6·4. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·3%), rapidly decolorising permanganate in cold alkaline solution. Reduction of this dihydro-acid was effected in acetic acid solution by hydrogen in presence of palladised charcoal; the corresponding ***tetrahydronaphthalene*-3-*carboxylic acid*** separated from methyl alcohol in silky needles, m. p. 162° (Found : C, 68·1; H, 6·9. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%), which were unaffected by cold permanganate. The corresponding acid chloride was not obtained pure, and Rosenmund reduction to the aldehyde was not realised.

4-*Keto*-6 : 7-*dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—A mixture of concentrated sulphuric acid (11 c.c.) and glacial acetic acid (11 c.c.) was gradually added, with ice cooling, to a mixture of ethyl β-hydroxymethylenepropionate (4 g.), veratrole (10 g.), and glacial acetic acid. After 18 hours, water was added and the product, isolated with chloroform, was hydrolysed by refluxing for 2 hours with 10% methyl-alcoholic potassium hydroxide (35 c.c.). Removal of the solvent and acidification gave the crude acid (9 g.) which was refluxed with excess of thionyl chloride in chloroform. The solvent was evaporated, the residue dissolved in nitrobenzene (50 c.c.), and aluminium chloride (8 g.) added. After 12 hours, dilute sulphuric acid was added, and the nitrobenzene removed in steam. The ***ketone***, isolated with chloroform and washed with dilute sodium hydroxide, was distilled at 0·1 mm. (bath temp. 270°); the distillate (6 g.) crystallised from methyl alcohol in prisms, m. p. 137—138° (Found : C, 69·9; H, 6·5. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%), which gave a 2 : 4-dinitrophenylhydrazone, m. p. 270° (decomp.).

6 : 7-*Dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—The above ketone (1 g.) was reduced by Clemmensen's method, and the product was distilled at 0·01 mm. and crystallised first from aqueous acetone and then from ligroin; clumps of fine needles, m. p. 76° (Found : C, 73·2; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·2; H, 7·3%), were obtained, which dissolved in concentrated sulphuric acid to give a bright red solution. When nitric acid was added to an acetic acid solution of the tetrahydronaphthalene, a reddish purple colour was obtained which gradually changed through blue and green to orange. Dehydrogenation with lead tetra-acetate in acetic acid solution gave 6 : 7-dimethoxy-1-veratrylnaphthalene, m. p. 160°.

ββ*-*Diveratryl*-*α*-*methylpropionic Acid (VI).—A mixture of concentrated sulphuric acid (32·5 c.c.) and glacial acetic acid (32·5 c.c.) was added to a cooled solution of ethyl α-hydroxymethylenepropionate (13 g.) and veratrole (30 g.) in acetic acid (25 c.c.). After 12 hours the oily product, isolated with chloroform, was hydrolysed by refluxing for 2 hours with 10% methyl-alcoholic potassium hydroxide (100 c.c.). The ***acid*** (VI) crystallised from ethyl acetate in nodules of needles, m. p. 175° (Found : C, 66·7; H, 6·7; equiv., 362. $C_{22}H_{24}O_6$ requires C, 66·7; H, 6·7%; equiv., 360).

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methylhydrindone* (VII).—The above acid (VI) (5·5 g.), in chloroform (50 c.c.), and thionyl chloride (3·5 g.) were refluxed for 1 hour, and the solvent removed in a vacuum. Aluminium chloride (5·5 g.) was gradually added with cooling to a solution of the residue in nitrobenzene (50 c.c.) and, after 12 hours, the mixture was decomposed and the nitrobenzene removed in steam. The product, isolated with ether and washed with sodium hydroxide solution, crystallised from methyl alcohol in large prisms (5 g.), m. p. 116° (Found : C, 69·9; H, 6·4. $C_{20}H_{22}O_5$ requires C, 70·1; H, 6·4%), yielding an ***oxime***, which separated from methyl alcohol in long glistening needles, m. p. 149—150° (Found : C, 67·3; H, 6·4. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4%).

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methyl*-1-*indone* (VIII).—The hydrindone (VII) (0·5 g.) and palladium black (0·1 g.) were heated for 1 hour at 250°, and the product was extracted with hot alcohol. Concentration of the extract gave orange-red prisms (0·05 g.), m. p. 189—192°, raised by recrystallisation from alcohol to 194—195°, undepressed by admixture with a specimen of the red compound, m. p. 193°, obtained by Haworth and Mavin (*loc. cit.*). The synthetic indone (VIII), and the product obtained by oxidation of di*iso*eugenol dimethyl ether, both dissolved in concentrated sulphuric acid to deep purple solutions.

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methylhydrindene* (IX).—The hydrindone (VII) (4 g.) was reduced by Clemmensen's method; the product (3 g.) crystallised from methyl alcohol in long colourless needles, m. p. 117° (Found : C, 73·3; H, 7·4. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·3%) depressed to 102° when mixed with a specimen of the ketone (VII). The ***hydrindene*** (IX) lacked ketonic properties, dissolved in concentrated sulphuric acid to a yellow solution, and gave the colour reaction described on p. 950. Dehydrogenation with selenium or lead tetra-acetate did not yield recognisable products.

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methyl*-1-*ethylindene* (X).—The hydrindone (VII) (5 g.) in benzene (50 c.c.) was gradually added to a solution of ethylmagnesium iodide, prepared from magnesium (1·0 g.) and ethyl iodide (7·5 c.c.) in ether (50 c.c.). After decomposition with ice and ammonium chloride, the product was heated at 180° for ½ hour with an equal weight of potassium hydrogen sulphate. The ***indene*** derivative (X), isolated with ether and washed with sodium bicarbonate solution, was obtained as a pale yellow resin, b. p. 195°/0·005 mm. (Found : C, 75·3; H, 7·7. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%), which reacted with ethylmagnesium iodide with formation of a precipitate and the evolution of ethane.

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methyl*-1-*ethylhydrindene* (IV; R = H).—The indene derivative (X) (0·5 g.) in glacial acetic acid (10 c.c.) was shaken with hydrogen in the presence of freshly prepared Adams's platinic oxide catalyst (0·05 g.). The theoretical volume of hydrogen was absorbed in ½ hour. After filtration from the catalyst, water was added and the product was isolated with ether, and washed with sodium bicarbonate solution. Removal of the ether left an oil which rapidly solidified and then crystallised from methyl alcohol in elongated prisms, m. p. 105° (Found : C, 74·0; H, 8·1. $C_{22}H_{28}O_4$ requires C, 74·2; H, 7·9%) depressed to 95—98° when mixed with di*iso*eugenol dimethyl ether.* The

* *Note, added 12th October, 1946.—Chemical Abstracts*, 1946, **40**, pp. 5041—5043, which has just been received, contains summaries of two additional papers by Müller and his co-workers, but the original papers (*Ber.*, 1944, **77**, 325, 343) are not available. In the second of these papers Müller describes the synthesis, by methods similar to ours, of the hydrindene (IV; R = Me), m. p. 105—106°. No mention of a direct comparison between the synthetic product and di*iso*eugenol dimethyl ether is included in the abstract, but, contrary to our observations, the title of the paper implies that identity is claimed.—R. D. H.

product, which did not decolorise permanganate in hot or cold acetone solution, was recovered after refluxing with methyl-alcoholic hydrogen chloride for 1½ hours. It dissolved in concentrated sulphuric acid to an orange solution with a green fluorescence, and when a drop of concentrated nitric acid was added to its solution in glacial acetic acid, a red colouration with a purple reflex was obtained, which gradually changed to a pure cherry-red colour. Dehydrogenation with lead tetra-acetate in acetic acid or selenium at 280° yielded either unchanged material or unrecognisable tars.

Our thanks are due to the West Riding Education Committee for a Scholarship.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, October 14th*, 1946.]

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179. *Substituted Benzilic Acids and Benzophenones.*

By A. H. FORD-MOORE.

A method for preparing substituted benzilic acids is described. Since these acids can be oxidised smoothly to the corresponding benzophenone, a number of the latter compounds which cannot be prepared by the Friedel–Crafts method are made available. The ethochlorides of the dimethylaminoethyl esters of some of these acids have been prepared, and their mydriatic activity measured against atropine sulphate.

IN a recent paper (Ford-Moore and Ing, this vol., p. 55), a number of synthetic mydriatics was described. One of these compounds, benzilyloxyethyldimethylethylammonium chloride (I; $R_1 = R_2 = Ph$), for which the name " Lachesine " has been suggested, was found to have a mydriatic activity equal to that of atropine sulphate. Certain other compounds in which

$$CR_1R_2(OH)\cdot CO_2\cdot CH_2\cdot CH_2\cdot NMe_2Et)Cl \qquad (I.)$$

substituents were introduced into the benzene nuclei of (I) were also prepared but were not then described. The result of this substitution was to reduce greatly, or even to abolish, the mydriatic activity of the compound.

This paper describes the preparation of the substituted benzilic acids used. These are mainly symmetrically disubstituted acids, but two monosubstituted acids were prepared and are included.

Two methods are available for the preparation of benzilic acids; oxidation of a benzoin with bromate and alkali, and treatment of a benzil with aqueous-alcoholic potash. Since the benzoins of substituted benzaldehydes could not usually be made to solidify, whereas the corresponding benzils were highly crystalline, the second method was adopted. Most of the substituted benzils are, however, so sparingly soluble in aqueous-alcoholic potash that conversion into the benzilic acid either takes place very slowly or not at all. Since these acids decarboxylate somewhat readily to give the benzhydrol, it is not safe to prolong the potash treatment for more than ten minutes.

Rearrangement of the substituted benzils can be brought about very readily by heating for ten minutes or less with a 20% solution of potassium hydroxide in hot *n*-butanol. In certain cases, the potassium salt of the acid separates out and only requires to be filtered off, washed with a little ether, dissolved in water, and acidified. Where the potassium salt is soluble in butanol, it can be extracted with water, a little ether being added to facilitate separation into two layers.

When the aqueous solution of the potassium salt is acidified, there is a strong tendency for the acid to separate in an obstinately gummy condition. Crystallisation can usually be induced by adding a small amount of a suitable solvent (benzene or petrol) and scratching. Seed, if available, will greatly hasten solidification.

The substituted benzilic acids are oxidised smoothly and in good yield by chromic anhydride in acetic acid to the corresponding benzophenone (cf. Jena, *Annalen*, 1870, **155**, 83). A number of the latter compounds, which cannot be prepared by the usual Friedel–Crafts method, are therefore made available.

Two monosubstituted benzilic acids, *viz.*, phenyl-α-naphthyl- and phenyl-β-naphthyl-glycollic acids, were described by Ford-Moore and Ing (*loc. cit.*). The same method as had been used for preparing these acids, *viz.*, *via* the deoxybenzoin, the *iso*nitroso-derivative, and the benzil, was adopted for preparing phenyl-*p*-tolylglycollic acid and 4-chlorobenzilic acid. The monosubstituted benzils, obtained in the penultimate step, are much more soluble in aqueous-alcoholic potash than are the disubstituted benzils, and no difficulty was experienced in converting them into the corresponding benzilic acids by means of this reagent.

Mydriatics from Substituted Benzilic Acids.—These compounds were made by the same method as was used for preparing (I), *i.e.*, treatment of β-chloroethyldimethylethylammonium chloride with the potassium salt of the acid in ethanol (Ford-Moore and Ing, *loc. cit.*). The compounds so obtained were useless as mydriatics. Nevertheless, they serve to illustrate the striking decrease in mydriatic activity on introducing substituents into the benzilyloxy-moiety of (I).

Experimental.

2 : 2′-*Dimethoxybenzilic Acid.*—*o*-Anisil (2 : 2′-dimethoxybenzil) (35 g.) was added to a solution of potassium hydroxide (17 g.) in boiling *n*-butanol (90 c.c.), and the mixture refluxed for 10 minutes. After cooling, the mixture was extracted three times with 100-c.c. portions of water, some ether being added to facilitate separation into two layers. The combined aqueous extracts were extracted once with ether (50 c.c.) to remove any dissolved butanol, freed from ether with a current of air, and acidified to Congo-red with hydrochloric acid. The *dimethoxybenzilic acid* was precipitated as a sticky mass which, if it did not solidify rapidly, could be made to do so by decanting the water, adding about 20 c.c. of benzene, and scratching. The yield was 33 g., m. p. 160°, after crystallising from methanol (Found : C, 66·4; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%).

Piperonilic (3 : 4-3′ : 4′-*bismethylenedioxybenzilic*) *acid*, m. p. 139° from ethyl acetate (Found : C, 61·0; H, 4·0. $C_{16}H_{12}O_7$ requires C, 60·8; H, 3·8%), 4 : 4′-dimethoxybenzilic acid, m. p. 171° (decomp.), from methanol (Bösler, *Ber.*, 1881, **14**, 327, gives 164°) (Found : C, 66·35; H, 5·7. Calc. for $C_{16}H_{16}O_5$: C, 66·6; H, 5·6%), and 3 : 3′-dichlorobenzilic acid, m. p. 110° from benzene–petrol (Klimont, Diss., Heidelberg, 1891, gives 114—115°) (Found : C, 56·4; H, 3·4. Calc. for $C_{14}H_{10}O_3Cl_2$: C, 56·55; H, 3·35%), were prepared similarly. The last compound was rather reluctant to crystallise but could be made to do so by adding petrol (b. p. 40—60°) and scratching.

5 : 5′-*Dibromo*-2 : 2′-*dimethoxybenzilic Acid.*—The corresponding benzil (cf. Kuhn, Birkofer, and Möller, *Ber.*, 1943, **76**, 903), m. p. 231° (20 g.), was treated with potash–butanol (7 g.; 40 c.c.) as for the dimethoxybenzil. On cooling, the potassium salt of the acid separated. It was filtered off, washed free from butanol with ether, and freed from ether by standing in the air for a short time. It was dissolved in water and acidified with hydrochloric acid; yield, 18 g., m. p. 181°, after crystallising from methanol (Found : C, 42·9; H, 3·25. $C_{16}H_{14}O_5Br_2$ requires C, 43·1; H, 3·15%).

Veratrilic acid (3 : 3′ : 4 : 4′-tetramethoxybenzilic acid) was prepared similarly; it melted at 131° after crystallising from ethyl acetate (Vanzetti, *Atti R. Accad. Lincei*, 1936, **24**, II, 468, gives *ca.* 68°) (Found : C, 61·9; H, 5·8. Calc. for $C_{18}H_{20}O_7$: C, 62·05; H, 5·8%).

These acids show a tendency to undergo partial decarboxylation. The benzhydrol so formed is difficult to remove by recrystallisation. Purification is readily effected by dissolution in dilute sodium carbonate solution, filtration (carbon), acidification, and crystallisation from a suitable solvent.

2 : 2′-*Dimethoxybenzophenone.*—2 : 2′-Dimethoxybenzilic acid (21·5 g.) was dissolved in boiling glacial acetic acid (100 c.c.) and oxidised by gradual addition of powdered chromic anhydride (5·5 g.). The reaction proceeded without the application of heat. When it was complete (10 mins.), the mixture was poured into water. The ketone, which rapidly solidified, was filtered off and washed free from chromium salts successively with water, dilute sodium carbonate, and water; yield 15 g., m. p. 103°, after crystallising from methanol (Graebe and Feer, *Ber.*, 1896, **19**, 2610, give 104°; Richter, *J. pr. Chem.*, 1883, **28**, 287, gives 98°).

3 : 3′ : 4 : 4′-Tetramethoxybenzophenone, m. p. 147° from ethanol (Kostanecki and Tambor, *Ber.*, 1906, **39**, 4027, give 145°), 5 : 5′-dibromo-2 : 2′-dimethoxybenzophenone, m. p. 128° (Diels and Rosenmund, *ibid.*, p. 2362, give 123°), and 3 : 3′-*dichlorobenzophenone*, m. p. 123—124° from methanol (Found : C, 62·3; H, 3·5. $C_{13}H_8OCl_2$ requires C, 62·2; H, 3·2%), were prepared similarly from the appropriate benzilic acid.

4-*Chlorobenzilic acid* and phenyl-*p*-tolylglycollic acid were prepared by the method described in the text. The former melted at 131° (Found : C, 64·1; H, 4·45. $C_{14}H_{11}O_3Cl$ requires C, 64·0; H, 4·2%), and the latter at 132° (Weiss, *Monatsh.*, 1919, **40**, 396, gives 131—133°), both having been crystallised from benzene.

Colour with Concentrated Sulphuric Acid.—The benzilic acids described above gave the following colours with concentrated sulphuric acid : 2 : 2′-dimethoxy-, brilliant greenish-blue; 4 : 4′-dimethoxy-, brilliant bluish-green; 3 : 3′ : 4 : 4′-tetramethoxy-, brilliant bluish-green; 3 : 4-3′ : 4-bis-methylenedioxy-, dark greenish-brown; 5 : 5′-dibromo-2 : 2′-dimethoxy-, brilliant bluish-green; 3 : 3′-dichloro-, violet; 4-chloro-, orange-red; phenyl-*p*-tolylglycollic acid, dark reddish-brown.

*Dimethylaminoethyl ester ethochlorides and their mydriatic activity.**

Serial number.	In (I) : R_1 =	R_2 =	M. p.†	Analysis, %. Found : C.	H.	Reqd. : C.	H.	R.M.P.‡
E19	3 : 4-CH_2O_2:C_6H_3		225° (d.)	58·30	5·77	58·46	5·80	0
E18	*p*-OMe·C_6H_4	*p*-OMe·C_6H_4	136°	62·54	7·28	62·36	7·08	8
E20	*m*-Cl·C_6H_4	*m*-Cl·C_6H_4	218—220° (d.)	55·61	5·50	55·50	5·59	0
E24	*p*-Me·C_6H_4	Ph	189—190°	67·00	7·44	66·75	7·47	16
E23	*p*-Cl·C_6H_4	Ph	196—197°	60·33	6·37	60·32	6·33	0

* Cf. Ford-Moore and Ing (*loc. cit.*).
† The solvent used for recrystallisation was ethanol–acetone.
‡ Relative molar potency (atropine sulphate = 100) on mouse eye.

The microanalyses were carried out by Mr. W. Brown and by Messrs. Weiler and Strauss.

The work described in this paper, which is published by permission of the Director General of Scientific Research (Defence), Ministry of Supply, was carried out while the author was a member of Sir Robert Robinson's team in the Dyson Perrins Laboratory, Oxford.

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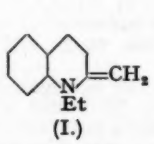
[*Received, October 23rd*, 1946.]

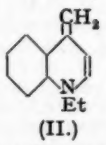
180. *Some Heterocyclic Methylene Bases and their Anilomethyl Derivatives.*

By FRANCES M. HAMER, RUSSELL J. RATHBONE, and BARBARA S. WINTON.

Some heterocyclic methylene bases, not hitherto described in the solid state, have been prepared by the action of alkali on quaternary salts at a low temperature, foregoing extraction. Some new anilomethyl derivatives of bases of this type were prepared by the action of alkali on quaternary salts having a 2-β-anilinovinyl group. They include anilomethyl derivatives of methylene bases derived from a benzoxazolium salt and a thiazolium salt, although the unsubstituted bases of these series are not precipitable. A practical method of preparation of ethyl*iso*formanilide is described. These compounds were made as starting materials for the synthesis of neocyanine and related dyes.

By treating quinaldine ethiodide with aqueous alkali, Vongerichten and Höfchen obtained an oil, which they regarded as the methylene base (I); they showed that it reacted with quinoline ethiodide to give a cyanine dye (*Ber.*, 1908, **41**, 3054). König expressed the opinion that bases such as (I) and (II) play an essential part in the formation of cyanines (*Ber.*, 1922, **55**, 3293).


(I.)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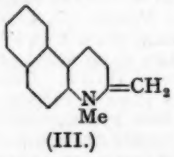
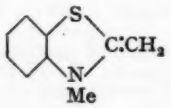

(III.)

Mills and Raper, considering that the oils formed by the action of alkali on quinaldine alkiodides could not be obtained analytically pure, examined the crystalline product (III) (*J.*, 1925, **127**, 2466); this led Rosenhauer (with Hoffmann and Unger) to record his preparation of the methyl analogue of (I) (*Ber.*, 1926, **59**, 946). From 2-methylbenzthiazole methoperchlorate König and Meier obtained (IV) (*J. pr. Chem.*, 1925, **109**, 324). Clark studied the conditions favouring formation of this base or of the thiophenol salt (V) and similarly, from 2-methylbenzselenazole methiodide, obtained two products, one of which was (VI) (*J.*, 1928, 2313).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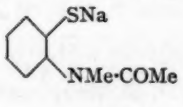
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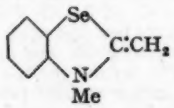
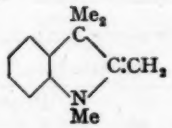
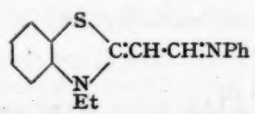

(VI.)

All these methylene bases were prepared from known quaternary salts but (VII), the first to be known, was made by direct synthesis (Fischer and Steche, *Annalen*, 1887, **242**, 348; Brunner, *Ber.*, 1898, **31**, 612).

(VII.) 


(VIII.)

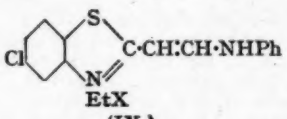
In our work on the synthesis of neocyanines, the methylene bases are of interest as starting points. In the patent literature Brooker and White have described anilomethyl derivatives, *e.g.* (VIII), of some such bases (Kodak Ltd., B.P. 561,172/1940) and these also have the same interest. The present paper deals with methylene bases and their anilomethyl derivatives.

Success in preparing methylene bases, hitherto inaccessible in the solid state, was achieved by precipitating them at a low temperature, by the action of alkali on a solution of the quaternary salt, and foregoing extraction with a solvent. We began by making the *ethyl* analogue of (IV), choosing a readily soluble quaternary salt of 2-methylbenzthiazole; it was

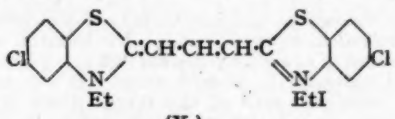
liable to manifest its instability by decomposing during drying but we succeeded in recrystallising both it and its 5-*chloro*-derivative. Its 6 : 7-*benz*-derivative showed a greater tendency to decompose and was not recrystallised; in preparing this and the *ethyl* analogue of (VI), aqueous suspensions of the quaternary salts were perforce used in place of concentrated solutions. From concentrated solutions of alko-*p*-toluenesulphonates, (I) and (II) were prepared. Colour changes, which indicate reactivity and tendency to cyanine dye formation on the part of the bases, occurred before they could be filtered off but did not proceed progressively after they had been dried.

Quaternary salts of certain other heterocyclic bases that are of interest in cyanine dye condensations do not give precipitates of methylene bases when their cold solutions are treated with alkali; such are salts of 2-methylbenzoxazole, 2 : 4-dimethylthiazole, 2-methylthiazoline, and α-picoline. In the different series of salts it appears that there is more than one cause for this. In the pyridine series, the base may possibly be too soluble and more complex methylene bases of this series have in fact been prepared (Mumm and Hingst, *Ber.*, 1923, **56**, 2301). In the benzoxazole series, it is due to fission of the ring, as recognised by Kŏnig and Meier (*J. pr. Chem.*, 1925, **109**, 324).

In preparing the anilomethyl derivative (VIII) of the ethyl analogue of (IV) from 2-β-anilinovinylbenzthiazole ethiodide, the method of the patent (Kodak Ltd., B.P. 561,172/1940) was adopted with some modification. In preparing 5-*chloro*-2-β-*anilinovinylbenzthiazole ethiodide* (IX; X = I), in order to make the 5-chloro-analogue of (VIII), the salt was accompanied by so much *thiacarbocyanine* (X) as by-product that we were forced, in order to get rid of the dye, first to isolate the pure 5-*chloro*-analogue of (VIII), from which we prepared the pure *ethochloride* (IX; X = Cl), and ultimately from that the pure *ethiodide* (IX; X = I). We prepared the 6-*nitro*-derivative of (VIII), starting from the product of nitration of 2-methylbenzthiazole



(IX.)

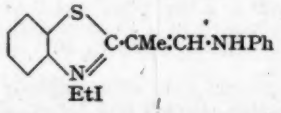


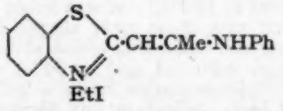
(X.)

(Browning, Cohen, Ellingworth, and Gulbransen, *Proc. Roy. Soc.*, 1931, *B*, **108**, 119; for orientation of the nitration product see Brooker, Keyes, and Williams, *J. Amer. Chem. Soc.*, 1942, **64**, 199). The 6-nitro-2-methylbenzthiazole was converted into its *metho*-p-*toluenesulphonate*; this was condensed with ethyl*iso*formanilide (cf. Knott, *J.*, 1946, 120), and the resultant *salt* treated with alkali to give the desired *base*.

To synthesise the α-*methyl* derivative of (VIII), 2-ethylbenzthiazole, prepared by two hitherto unpublished methods, was converted into its *etho*-p-*toluenesulphonate* and this was condensed with diphenylformamidine, or better with ethyl*iso*formanilide, and the product treated with

(XI.)

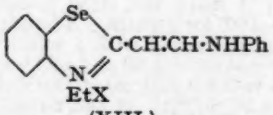




(XII.)

potassium iodide to give (XI), whence the *base* was liberated by the action of alkali. We also prepared the β-*methyl* derivative of (VIII) by the action of alkali on the quaternary salt (XII).

In the preparation of the *selenium* analogue of (VIII), from the *quaternary salt* (XIII; X = I), the product refused to solidify, but after treatment with hydrochloric acid to give the *ethochloride* (XIII; X = Cl) it was possible to obtain the solid base by the action of alkali. In the quinoline series we prepared (XIV), the ethyl analogue of which has been described (Kodak Ltd., B.P. 561,172/1940). Particularly interesting is the record in the patent that the anilomethyl derivative of a methylene base of the thiazoline series was prepared, since the



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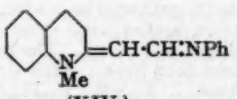
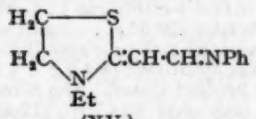


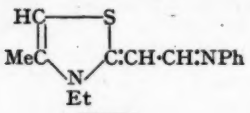
(XIV.)



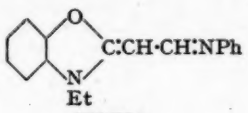
(XV.)

unsubstituted methylene base of this series is one of those not precipitable by the action of alkali on the quaternary salt. We were also able to prepare the corresponding *ethyl* analogue (XV), by applying different conditions, and the *anilomethyl* derivatives, (XVI) and (XVII), of

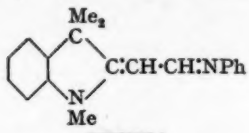
methylene bases of a thiazole series and of the benzoxazole series, respectively, where again the parent unsubstituted bases have not been described.



(XVI.)



(XVII.)



(XVIII.)

To obtain the *anilomethyl* derivative (XVIII) of the methylene base (VII), 2-β-anilinovinyl-3 : 3-dimethylindolenine methiodide was acted on, in benzene suspension, by aqueous alkali. The quaternary salt was originally prepared either by hydrolysing the corresponding acetanilidovinyl compound or else by heating 1 : 3 : 3-trimethylindolenine methiodide with diphenylformamidine (I.C.I. Ltd., Piggott, and Rodd, B.P. 344,409/1929), but we used ethyl*iso*formanilide instead of diphenylformamidine.

Ethyl*iso*formanilide was required for the present work and also for our synthesis of neocyanine, so that its large-scale production became a matter of interest. Claisen's methods for preparing it were to condense ethyl orthoformate (1) with aniline, (2) with diphenylformamidine, or (3) with formanilide in the presence of aniline hydrochloride (*Annalen*, 1895, **287**, 362). Monier-Williams (*J.*, 1906, **89**, 273) preferred to use the method of Comstock and Kleeburg (*Amer. Chem. J.*, 1890, **12**, 497) and treated dry silver *iso*formanilide with ethyl iodide in absolute ether. This last did not seem practicable on a large scale and we worked out a modification of Claisen's first method, including aniline hydrochloride in order to inhibit the formation of carbylamine.

Experimental.

3-Ethyl-2-methylenebenzthiazoline.—2-Methylbenzthiazole etho-*p*-toluenesulphonate (50 g.; 1 mol.) was dissolved in water (70 c.c.). The solution was cooled with ice and stirred during the addition of a cold solution of sodium hydroxide (6·3 g.; 1·1 mols.) in water (20 c.c.). The white solid was filtered off, and well washed with ice-cold water. It was dried in a vacuum desiccator and obtained in 83% yield (21 g.), being pale pink at this stage. Once dry, it kept for weeks without further deterioration but preparations on a larger scale were apt to decompose during drying. On recrystallisation from light petroleum (b. p. 80—100°; 20 c.c. per g.), the yield was 62%. After drying in a vacuum desiccator, it was analysed by the method of Carius, which method was used throughout this work (Found: S, 18·15. $C_{10}H_{11}NS$ requires S, 18·1%); m. p. 126—128° (decomp.).

5-Chloro-3-ethyl-2-methylenebenzthiazoline.—Similarly, 5-chloro-2-methylbenzthiazole etho-*p*-toluenesulphonate gave the *base* in 87% yield; on recrystallisation from light petroleum (b. p. 80—100°; 275 c.c. per g.), it fell to 57% (Found, after drying in a vacuum desiccator: Cl, 16·45; S, 15·1. $C_{10}H_{10}NClS$ requires Cl, 16·75; S, 15·15%). The chalky white solid had m. p. 178—180° (decomp.).

3-Ethyl-2-methylene-6 : 7-benzbenzthiazoline.—2-Methyl-6 : 7-benzbenzthiazole etho-*p*-toluenesulphonate (30 g.; 1 mol.) was ground to a paste with ice-cold water (30 c.c.), and an ice-cold solution of sodium hydroxide (3·3 g.; 1·1 mols.) in water (10 c.c.) was added. The sulphur-yellow solid was thoroughly washed with ice-cold water and was obtained in 68% yield (11·65 g.) (Found: S, 14·55. $C_{14}H_{13}NS$ requires S, 14·1%); it was liable to change overnight to a sticky mass at the early stages of drying but, once past those early stages, could be kept unchanged in a vacuum desiccator. When heated, shrinking and darkening began about 40° and it was brown and sticky by 50°; gradual melting and decomposition occurred, and by 90° it was a brown liquid.

3-Ethyl-2-methylenebenzselenazoline.—2-Methylbenzselenazole ethiodide when similarly treated gave a 76% yield of *base*. Selenium was determined as silver selenite (Becker and Meyer, *Ber.*, 1904, **37**, 2550) (Found: Se, 35·45. $C_{10}H_{11}NSe$ requires Se, 35·3%). The yellowish-brown powder softened from 70° and decomposed at about 120°. One specimen, which had been kept for several days in a vacuum desiccator without change, became sticky and dark overnight, although the vacuum had been maintained.

1-Ethyl-2-methylene-1 : 2-dihydroquinoline (I).—Quinaldine etho-*p*-toluenesulphonate (34·33 g.; 1 mol.), dissolved in ice-cold water (30 c.c.), was treated with ice-cold aqueous sodium hydroxide solution (4·4 g., 1·1 mols., in 11 c.c.). The buff precipitate was filtered off and thoroughly washed with ice-cold water. After drying in a vacuum desiccator, it was obtained in 78% yield (13·37 g.), and was then brick-red (Found: N, 7·95. $C_{12}H_{13}N$ requires N, 8·2%); m. p. 79° (decomp.) with previous softening. A sample which had been kept in a vacuum desiccator for a fortnight appeared to be unchanged.

1-Ethyl-4-methylene-1 : 4-dihydroquinoline (II).—Lepidine (14·31 g.; 1 mol.) and ethyl *p*-toluenesulphonate (20·02 g.; 1 mol.) were heated together in an oil-bath at 155—160° for 3 hours. A solution of the viscous salt in water (32 c.c.) was extracted with ether, then treated ice-cold with a solution of sodium hydroxide (4·4 g.; 1·1 mols.) in water (11 c.c.). The precipitate was filtered off and well washed with ice-cold water. The filtrate became deep blue. After drying in a vacuum desiccator, the yield of pale blue *solid* was 73% (12·55 g.) (Found: N, 8·2. $C_{12}H_{13}N$ requires N, 8·2%). It had no definite m. p. On heating, shrinking began at 59°; in one case, with slow heating, it was black and molten by 80°, whilst in another, violent frothing occurred between 95° and 108°.

3-Ethyl-2-aniloethylidenebenzthiazoline (VIII).—The published method (Kodak Ltd., B.P. 561,172/1940) was varied in that the suspension of 2-β-anilinovinylbenzthiazole ethiodide (103 g.; 1 mol.) in acetone (940 c.c.) was shaken with a solution of sodium hydroxide (31 g.; 3 mols.) in water (75 c.c.), instead of

being stirred mechanically. In one instance solution occurred, but in another, very much more acetone (11·4 l.) had to be added, this indicating the conversion of a less stable into a more stable form. The acetone extracts were filtered, with removal of bis-2-(3-ethylbenzthiazole)trimethincyanine iodide (5·81 g.), which was recrystallised from methyl alcohol (75 c.c. per g.; 2·7 g. obtained) and dried in a vacuum at 60—80°, which conditions of drying were used throughout this work, except where otherwise stated (Found: I, 25·95. Calc. for $C_{21}H_{21}N_2IS_2$: I, 25·8%). On pouring the acetone filtrate into its own volume of water, the base was precipitated in 70% yield (49 g.). Two recrystallisations from light petroleum (b. p. 80—100°; 100 c.c. per g.) reduced the yield to 43% (Found, after drying in a vacuum desiccator: S, 11·25. Calc. for $C_{17}H_{16}N_2S$: S, 11·45%). The yellow solid had m. p. 79°, whereas the m. p. quoted in the patent is 98—99° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3935 A. and of one containing sulphuric acid at 4175 A.

5-Chloro-3-ethyl-2-aniloethylidenebenzthiazoline.—5-Chloro-2-methylbenzthiazole ethiodide (20 g.; 1 mol.) and ethyl*iso*formanilide (7 g.; 1 mol.) were heated together with stirring at 140—150° for 1 hour. The product was boiled with spirit (300 c.c.), and the crystals were filtered off after cooling (22 g. obtained). An attempt to separate the quaternary salt from the dye by-product by boiling out five times with spirit (2 × 100 c.c., 2 × 150 c.c., 250 c.c.) left a dye residue (5·69 g.), and a 36% yield (9·43 g.) of impure salt crystallised from the extracts. The dye was further boiled out twice with methyl alcohol (50 c.c., 100 c.c.) and the residue (4·96 g.) suspended in acetone (38 c.c.) and shaken with a solution of sodium hydroxide (1·35 g.) in water (5 c.c.), with the object of converting any contaminating salt into base. After two more acetone extractions, the residual dye was well washed with water (3·46 g. obtained) and recrystallised from methyl alcohol (1590 c.c.) (2·81 g. obtained) (Found: 2Cl + I, 35·45. $C_{21}H_{19}N_2Cl_2IS_2$ requires 2Cl + I, 35·25%). The blue needles of *bis-2-(5-chloro-3-ethylbenzthiazole)trimethincyanine iodide* (X) did not melt below 270°. The absorption maximum was at 5625 A. It sensitised a gelatino-bromide photographic emulsion from 5200 to 6200 A., with a maximum at 6000 A. The impure quaternary salt (9·43 g.; 1 mol.) was suspended in acetone (70 c.c.), and the ice-cold solution shaken with one of sodium hydroxide (2·56 g.; 3 mols.) in water (10 c.c.). The acetone extract was filtered and the aqueous part further extracted with acetone, dye by-product being left undissolved. The extracts were precipitated with thrice their volume of water and the resultant solid was obtained in 83% yield (5·57 g.). After recrystallisation from methyl alcohol (335 c.c.) the yield was 70% (Found: Cl, 11·45. $C_{17}H_{15}N_2ClS$ requires Cl, 11·3%). The yellowish-green powder had m. p. 138°. The absorption maximum of a methyl-alcoholic solution containing pyridine was at 4075 A. and of one containing sulphuric acid at 4205 A. The dye sensitised a chloride emulsion to 4900 A. with the maximum at 4600 A.

5-Chloro-2-β-anilinovinylbenzthiazole Ethochloride (IX; X = Cl).—5-Chloro-3-ethyl-2-aniloethylidenebenzthiazoline (6·64 g.) was warmed with spirit (13 c.c.), and the suspension treated with concentrated hydrochloric acid (7 c.c.). The crystals which separated on cooling (7·49 g.) were recrystallised from methyl alcohol (60 c.c.) and obtained in 86% yield (6·36 g.) (Found: Cl, 20·2. $C_{17}H_{16}N_2Cl_2S$ requires Cl, 20·2%). The bright yellow powder became orange at 100°, was brown by 200°, and melted at 214—215° (decomp.).

5-Chloro-2-β-anilinovinylbenzthiazole Ethiodide (IX; X = I).—The *ethochloride* (IX; X = Cl) (0·45 g.; 1 mol.) was dissolved in hot spirit (15 c.c.) and added to a hot solution of potassium iodide (16·6 g.; 10 mols.) in water (30 c.c.). The crude *salt* (0·47 g.) was recrystallised from methyl alcohol (47 c.c. per g.) and obtained in 58% yield (0·33 g.) (Found: Cl + I, 36·8. $C_{17}H_{16}N_2ClIS$ requires Cl + I, 36·7%). The dark orange crystals had m. p. 241—244° (decomp.).

6-Nitro-2-methylbenzthiazole Metho-p-toluenesulphonate.—6-Nitro-2-methylbenzthiazole (2·77 g.; 1 mol.) and methyl *p*-toluenesulponate (2·66 g.; 1 mol.) were heated together at 130° for 1 hour, and the product was ground with absolute ether (5·16 g. obtained; 95%). After recrystallisation from absolute ethyl alcohol (10 c.c.), the yield was 88% (4·77 g.) (Found: S, 16·8. $C_{16}H_{16}O_5N_2S_2$ requires S, 16·85%). The cream-coloured crystals had m. p. 194—195° (decomp.).

6-Nitro-2-β-anilinovinylbenzthiazole Metho-p-toluenesulphonate.—The foregoing *metho-p-toluenesulphonate* (19 g.; 1 mol.) and ethyl*iso*formanilide (9 g.; 1·2 mols.) were heated and stirred together at 130—140°. Fusion occurred, then vigorous reaction followed by solidification. Heating was continued for ½ hour. A suspension of the solid in spirit (50 c.c.) was poured into warm water. The *product*, after being washed with water and with acetone (18 g. obtained), was recrystallised from methyl alcohol (200 c.c. per g.), the yield falling from 75% to 23% (Found: S, 13·45. $C_{23}H_{21}O_5N_3S_2$ requires S, 13·25%). The green crystals had m. p. 255°.

6-Nitro-3-methyl-2-aniloethylidenebenzthiazoline.—The preceding compound (9·66 g.; 1 mol.), acetone (300 c.c.), and 20% sodium hydroxide solution (20 c.c.; 5 mols.) were warmed together on the steam-bath, then shaken vigorously for several minutes. The filtered acetone layer was concentrated to one-third, and poured into ice and water (500 c.c.), coagulation being assisted by addition of ammonium chloride. The washed *product* (4·83 g.; 78%) was purified by dissolving in benzene (10 c.c. per g.), filtering, and precipitating with an equal volume of light petroleum (b. p. 80—100°); yield, 63% (Found: S, 10·45. $C_{16}H_{13}O_3N_3S$ requires S, 10·3%). The brick-red crystals had m. p. 144° (decomp.) and desensitised strongly. The broad absorption curve of a methyl-alcoholic solution containing ammonia had its maximum at 3850 A.

2-Ethylbenzthiazole.—This was originally prepared by heating *o*-aminothiophenol in a sealed tube with propionyl chloride, being characterised as its platinichloride (Hofmann, *Ber.*, 1880, **13**, 8). According to our first method, *o*-aminothiophenol hydrochloride (80·6 g.; 1 mol.) was treated with propionic anhydride (69·5 c.c.; 1·1 mols.) and with zinc dust (11·2 g.). The reaction was started by warming; after it had subsided, the mixture was heated on the steam-bath for 2 hours, and then made alkaline with sodium hydroxide and steam-distilled; the oil was extracted with chloroform, and the extract dried (Na_2SO_4). After removal of the solvent, the residue was distilled in a vacuum and obtained in 52% yield, b. p. 127—131°/6 mm. (Found: S, 19·8. Calc. for C_9H_9NS: S, 19·65%). Our second method consisted in preparing *o*-aminothiophenol from *o*-chloronitrobenzene (cf. I.G. Farbenind. A.-G., F.P. 669,921/1929; Société Anonyme des Matières Colorantes et Produits Chimiques de Saint-

Denis, F.P. 714,682/1930) and effecting the ring closure to 2-ethylbenzthiazole by means of propionic anhydride. *o*-Chloronitrobenzene (100 g.; 1 mol.), crystalline sodium sulphide (400 g.; 2·63 mols.), and water (400 c.c.) were stirred together, being warmed to start the reaction; after its vigour had abated, heating on the steam-bath and stirring were continued for 4 hours. The mixture was steam-distilled to remove *o*-chloroaniline, formed as a by-product (26 g.; 32%), then it was cooled, treated with a solution of propionic anhydride (83 g.; 1 mol.) in propionic acid (156 g.; 3·3 mols.), and heated under reflux for an hour on the steam-bath. It was cooled, made alkaline and extracted with ether. The extract was dried (Na_2SO_4), the solvent removed, and the residue distilled under a vacuum. After a second vacuum distillation the yield was 34% (35 g.), b. p. 112—114°/5 mm. (Found: S, 19·9%). The preparation according to the first method was carried out by Miss E. M. Wilson, and that according to the second by Mr. J. Fraser.

2-*Ethylbenzthiazole Etho*-p-*toluenesulphonate*.—2-Ethylbenzthiazole (4·08 g.; 1 mol.) and ethyl *p*-toluenesulphonate (5 g.; 1 mol.) were heated together at 140—150° for 2½ hours. The solidified melt was ground and washed with acetone, being obtained in 84% yield (7·55 g.) (Found: S, 17·8. $C_{18}H_{21}O_3NS_2$ requires S, 17·65%). The pale pink *solid* melted at 138°.

2-(*β-Anilino-α-methylvinyl*)*benzthiazole Ethiodide* (XI).—The preceding compound (5 g.; 1 mol.) and ethyl*iso*formanilide (2·3 g.; 1·1 mols.) were heated together at 120—140°, vigorous reaction then occurring. Heating was continued for ½ hour, and the red liquid was dissolved in spirit (7 c.c.) and treated with a hot solution of potassium iodide (8·26 g.; 4 mols.) in water (7 c.c.). The *iodide* crystallised and, after being washed, was obtained in 72% yield (4·3 g.), decreased on recrystallisation from ethyl alcohol (50 c.c. per g.) to 50% (Found: I, 30·1. $C_{18}H_{19}N_2IS$ requires I, 30·05%). The dull red crystals melted at 212° (decomp.).

When a similar preparation was carried out with diphenylformamidine instead of ethyl*iso*formanilide, the yield of crude washed product was only 24%. Neither diphenylformamidine nor ethyl*iso*formanilide gave a positive result when the starting point was 2-ethylbenzthiazole ethiodide instead of the etho-*p*-toluenesulphonate.

3-*Ethyl*-2-*anilo*iso*propylidenebenzthiazoline*.—2-(β-Anilino-α-methylvinyl)benzthiazole ethiodide (5·44 g.; 1 mol.), 20% sodium hydroxide solution (12 c.c.; 5 mols.), and acetone (150 c.c.) were stirred together and warmed on the water-bath, then shaken in a separating funnel. The filtered acetone layer was poured into ice-water. The aqueous liquid was decanted from the sticky solid, which on crystallisation from light petroleum (b. p. 80—100°; 75 c.c.) gave a 41% yield (1·57 g.) of yellow crystals, m. p. 92° (decomp.) (Found after drying in a vacuum at 50—60°: S, 10·85. $C_{18}H_{18}N_2S$ requires S, 10·9%). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4005 A. The *compound* sensitised a chloride emulsion fairly strongly with its maximum at 4550 A., sensitisation extending to 4850 A.

2-(*β-Anilino-β-methylvinyl*)*benzthiazole Ethiodide* (XII).—The steps in the following synthesis of the salt required as starting point were carried out according to directions supplied by Dr. L. G. S. Brooker: 2-methylbenzthiazole etho-*p*-toluenesulphonate was converted successively into 3-ethyl-2-acetylmethylenebenzthiazoline (Kodak Ltd., B.P. 466,269/1935), 2-β-chloropropenylbenzthiazole ethochloride (*idem*, B.P. 533,425/1939), 3-ethyl-2-thioacetylethylbenzthiazoline (*idem*, B.P. 546,705/1941), and 2-(β-methylthiopropenyl)benzthiazole etho-*p*-toluenesulphonate (*idem*, B.P. 538,857/1941). This last salt (66·1 g.; 1 mol.), aniline (19·7 g.; 1·25 mols.), and absolute alcohol (170 c.c.) were boiled together under reflux for 30 minutes. The yellowish-brown solution was poured into a hot solution of potassium iodide (56 g.; 2 mols.) in water (100 c.c.). The *iodide* was obtained in 84% yield (60·0 g.). On recrystallising twice from spirit (15 c.c. per g.), the yield dropped to 69% (Found: I, 30·25. $C_{18}H_{19}N_2IS$ requires I, 30·05%). The bright yellow crystals had m. p. 208° (decomp.).

3-*Ethyl*-2-*β-anilopropylidenebenzthiazoline*.—2-(β-Anilino-β-methylvinyl)benzthiazole ethiodide (8·44 g.; 1 mol.), suspended in acetone (250 c.c.), was stirred and warmed for a few minutes on the steam-bath with 20% sodium hydroxide solution (20 c.c.; 5 mols.), and the mixture shaken. The filtered acetone layer was poured into ice-cold water (1000 c.c.). The *solid* (5·5 g.) was recrystallised from light petroleum (b. p. 80—100°; 25 c.c. per g.), the yield then being 65% (3·85 g.) (Found: S, 10·7. $C_{18}H_{18}N_2S$ requires S, 10·9%). The pale yellow crystals had m. p. 114° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3670 A. The base was photographically inert.

2-*β-Anilinovinylbenzselenazole Ethiodide* (XIII; X = I).—2-Methylbenzselenazole ethiodide (28·2 g.; 1 mol.) and ethyl*iso*formanilide (13·2 g.; 1·1 mols.) were heated together at 150—160° for ½ hour. The *product* was ground with spirit (32·7 g. obtained); after recrystallisation from spirit (30 c.c. per g.) the yield was 59% (Found: I, 27·8. $C_{17}H_{17}N_2ISe$ requires I, 27·85%). The greenish-golden crystals had m. p. 222° (decomp.).

3-*Ethyl*-2-*aniloethylidenebenzselenazoline*.—The above ethiodide (32 g.; 1 mol.), ground to a paste with water, was treated with 40% sodium hydroxide solution (40 c.c.; 5 mols.) and acetone (500 c.c.). The mixture was slightly warmed, then well shaken. The filtered, concentrated acetone extract gave with dilute hydrochloric acid 2-*β-anilinovinylbenzselenazole ethochloride* (XIII; X = Cl), which, after recrystallisation from acetone–spirit (3 : 1, 30 c.c. per g.), was obtained in 55% yield (14·4 g.). Chlorine was determined by the method which has been found suitable for iodine in the presence of selenium (Hamer, *Analyst*, 1933, **58**, 26) (Found: Cl, 9·55. $C_{17}H_{17}N_2ClSe$ requires Cl, 9·75%). The bright yellow crystals had m. p. 205° (decomp.). They were dissolved in hot spirit, and the *base* precipitated by dilute ammonia (11·2 g.; 49%); it was recrystallised from light petroleum (b. p. 80—100°; 20 c.c. per g.) and the yield was 34% (7·8 g.) (Found: N, 8·55. $C_{17}H_{16}N_2Se$ requires N, 8·55%). The bright yellow crystals had m. p. 96°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3940 A. and of one containing sulphuric acid at 4235 A. For a chloride emulsion the base was a medium sensitiser, with the maximum at 4600 A., sensitisation extending to 5100 A.

1-*Methyl*-2-*aniloethylidenedihydroquinoline* (XIV).—2-β-Anilinovinylquinoline methiodide (7·76 g.; 1 mol.) was suspended in acetone (100 c.c.) and shaken for 12 minutes with a solution of sodium hydroxide (4 g.; 5 mols.) in water (50 c.c.). The filtered acetone layer with ice-cold water (600 c.c.) deposited the base in 97% yield (10·16 g.). On recrystallising from light petroleum (b. p. 80—100°)–benzene (1 : 1,

10 c.c. per g.), some tar was left undissolved and the yield fell to 62% (Found, after drying in a vacuum desiccator: N, 10·95. $C_{19}H_{16}N_2$ requires N, 10·75%). The bright orange crystals had m. p. 88° (decomp.). The absorption maximum of an alkaline methyl-alcoholic solution was at 4335 A. In a gelatino-chloride photographic emulsion, sensitisation extended to 5100 A., with a maximum at 4700 A.

3-Methyl-2-aniloethylidenethiazolidine.—This was prepared from 2-β-anilinovinylthiazoline methiodide and sodium hydroxide in aqueous acetone, followed by precipitation with water, as described (Kodak Ltd., B.P. 561,172/1940). The yield was 79%, dropping to 73% on recrystallisation from benzene (1 c.c. per g.) (Found, after drying to constant weight in a vacuum desiccator: S, 14·6. Calc. for $C_{12}H_{14}N_2S$: S, 14·7%). The m. p. was 79—80°, whereas that published is 99—100°.

3-Ethyl-2-aniloethylidenethiazolidine (XV).—2-β-Anilinovinylthiazoline ethiodide (36 g.; 1 mol.), benzene (800 c.c.), and 40% sodium hydroxide solution (80 c.c.; 8 mols.) were heated together under reflux on a steam-bath, with vigorous stirring, for 30 minutes. After the solvent had been distilled from the filtered benzene layer, the solid residue was recrystallised from light petroleum (b. p. 80—100°; 1000 c.c.) and obtained in 77% yield (18·0 g.) (Found, after drying in a vacuum desiccator: S, 13·75. $C_{13}H_{16}N_2S$ requires S, 13·8%). The cream-coloured *substance* had m. p. 65°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3585 A. with an inflexion to the curve at 3200 A.; one containing sulphuric acid had its maximum at 3660 A. On a gelatino-chloride photographic emulsion it conferred extra-sensitivity up to 4400 A.

4-Methyl-3-ethyl-2-aniloethylidene-Δ⁴-thiazoline (XVI).—4-Methyl-2-β-anilinovinylthiazole ethiodide (18·6 g.; 1 mol.) was ground with 20% sodium hydroxide solution (50 c.c.; 4 mols.). The mixture was stirred and warmed with acetone (250 c.c.). The crude product (23 g.), obtained by precipitation of the acetone layer with ice-water (1000 c.c.), was recrystallised from light petroleum (b. p. 80—100°) and benzene (2 : 1, 20 c.c. per g.). A 74% yield of golden crystals (18·0 g.) was obtained (Found: S, 12·95. $C_{14}H_{16}N_2S$ requires S, 13·1%); m. p. 122° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4090 A. and of one containing sulphuric acid at 4030 A. The *substance* sensitised a chloride emulsion fairly strongly, sensitisation extending to 4900 A., with the maximum at 4500 A.

3-Ethyl-2-aniloethylidenebenzoxazoline (XVII).—2-β-Anilinovinylbenzoxazole ethiodide (58·8 g.; 1 mol.), aqueous 40% sodium hydroxide solution (90 c.c.; 6 mols.), and benzene (1500 c.c.) were stirred together and warmed gently on a steam-bath, then shaken vigorously for several minutes. The benzene solution was filtered and distilled down to dryness: the resultant gum was taken up with acetone, and the *base* precipitated with water, being obtained in 58% yield (23 g.). Recrystallisation was difficult; benzene appeared to be the most suitable solvent (5 c.c. per g.) but the yield fell to 6% (Found, after drying in a vacuum desiccator: N, 10·5. $C_{17}H_{16}ON_2$ requires N, 10·6%). The pale yellow crystals had m. p. 65° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3660 A. and of one containing sulphuric acid at 3835 A. A gelatino-chloride photographic emulsion was weakly sensitised to 4400 A., with the maximum effect at 4200 A.

3 : 3-Dimethyl-2-β-anilinovinylindolenine Methiodide.—2 : 3 : 3-Trimethylindolenine methiodide (20 g.; 1 mol.) and ethyl*iso*formanilide (10 g.; 1 mol.) were heated together in an oil-bath at 140° for 40 minutes with continual breaking up of the lumpy solid. After dissolving in hot spirit (130 c.c.), the product crystallised in 75% yield (20 g.). It was boiled out with spirit (25 c.c.) and on recrystallising the residue from spirit (125 c.c.) the yield was 55% (Found: I, 31·35. Calc. for $C_{19}H_{21}N_2I$: I, 31·4%). The yellow crystals had m. p. 236—238° (decomp.).

1 : 3 : 3-Trimethyl-2-aniloethylideneindoline (XVIII).—The foregoing methiodide (3·91 g.; 1 mol.) was suspended in benzene (40 c.c.) and shaken with a solution of sodium hydroxide (1·16 g.; 3 mols.) in water (5 c.c.). Subsequently four more such benzene extractions were carried out. The benzene filtrate was taken to dryness and the residue twice recrystallised from light petroleum (b. p. 80—100°; 2 × 8 c.c.), the yields being 73% and 64% (1·70 g.) (Found, after drying in a vacuum desiccator: N, 10·0. $C_{19}H_{20}N_2$ requires N, 10·15%). The yellow powder had m. p. 89°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 3745 A. and of one containing sulphuric acid at 4120 A. It sensitised a gelatino-chloride photographic emulsion up to 4700 A.

*Ethyliso**formanilide.*—Ethyl orthoformate (1200 c.c.; 2 mols.), aniline (336 c.c.; 1 mol.), and aniline hydrochloride (36 g.) were boiled together in an oil-bath for 4 hours, in a flask fitted with fractionating column, condenser, and receiver to collect the alcohol eliminated. The temperature of the bath was kept at 120° until the first vigour of the reaction had subsided and was then raised to 140—150°. After cooling, any diphenylformamidine was filtered off, and the filtrate was fractionally distilled under a vacuum. After a forerun, b. p. 50—110°/20 mm., the ethyl*iso*formanilide was collected at 110—120°/20 mm. The foreruns from several batches were fractionated together, the fraction boiling up to 110°/20 mm. being used as ortho-ester for another preparation, and the fraction above 110°/20 mm. being refractionated with ethyl*iso*formanilide. As a result, the 85% yield from a second fractional distillation (504 g.) is slightly larger than that from the first fractionation (81% yield; 480 g.).

We are indebted to Miss M. D. Gauntlett for the absorption spectra, to Dr. B. H. Carroll and Dr. E. B. Knott for the photographic tests, and to Mr. J. Fraser and Miss E. M. Wilson for the preparations specified.

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181. *Symmetrical Tricarbocyanines having One or More Methyl Groups as Substituents on the Chain.*

By Frances M. Hamer and Russell J. Rathbone.

1-, 2-, and 3-Methyl derivatives of glutaconic aldehyde dianilide hydrohalide were prepared, also 1 : 5- and 1 : 3-dimethyl derivatives, from the appropriate pyridinium cyanobromides. They were condensed with heterocyclic quaternary salts to give tricarbocyanines having β-, γ-, and δ-methyl groups, also ββ′- and βδ-dimethyl groups on the chain. Absorption maxima and photographic sensitising action of the dyes are recorded.

In a patent on photographic sensitising action, the four examples of chain-substituted tricarbocyanines comprise one with a β-methyl and three with a δ-methyl group (I.G. Farbenind. A.-G., B.P. 394,537/1931). It is recorded that the intermediate for the first was prepared by König's method from β-naphthylamine, α-picoline, and cyanogen chloride in ether (*J. pr. Chem.*, 1904, **69**, 105), whilst that for the others was obtained analogously from aniline, γ-picoline, and cyanogen bromide. As no preparations whatever are described, we considered it desirable to record some.

Although König did originally describe the preparation of a dye from α-picoline, cyanogen chloride, and *o*-toluidine (*loc. cit.*), he subsequently disclaimed it but claimed that pure β-picoline does indeed form such a dye (*J. pr. Chem.*, 1904, **70**, 19). König and Schreckenbach (*ibid.*, 1913, **87**, 241) had found that 2 : 4-dinitrophenylpyridinium chloride does not, whilst pyridinium cyanobromide does, react with indoles to give dyes. α-Picoline and αα′-lutidine do not combine with 1-chloro-2 : 4-dinitrobenzene to give pyridinium salts but we made them react with cyanogen bromide and thence, with aniline and hydrobromic or hydrochloric acid, obtained *dyes* (I) and (II). Similarly from β-picoline we prepared (III), referred to (but not described) by König (*ibid.*, 1904, **70**, 19), and from γ-picoline we prepared (IV). The product derived from γ-lutidine was used in condensations but we did not isolate a pure specimen of (V).

HBr,NHPh·CMe:CH·CH:CH·CH:NPh (I.)

HCl,NHPh·CMe:CH·CH:CH·CMe:NPh (II.)

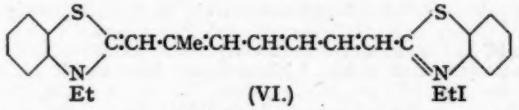
HBr,NHPh·CH:CMe·CH:CH·CH:NPh (III.)

HBr,NHPh·CH:CH·CMe:CH·CH:NPh (IV.)

HBr,NHPh·CMe:CH·CMe:CH·CH:NPh (V.)

We compared the absorption maxima of (I)—(IV) in methyl-alcoholic solution with that of the parent dye having an unsubstituted chain. In passing from the parent dye to (II) and (III), there were bathochromic shifts of the maximum, of 45 A. and 10 A., respectively, and hypsochromic shifts, of 90 A. and 65 A., respectively, in passing to (I) and (IV). Whereas the parent dye is a photographic sensitiser, (I) was distinctly weaker, whilst (II), (III), and (IV) showed no sensitising power.

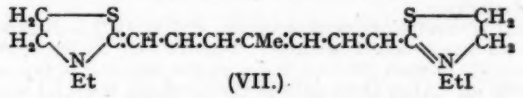
Glutaconic aldehyde dianilide hydrohalide condenses in the presence of sodium ethoxide, or of sodium acetate in acetic anhydride, with quaternary salts having reactive methyl groups to give tricarbocyanines (Fisher and Hamer, *J.*, 1933, 189), but these condensing agents seemed unsuitable for use with the present substituted intermediates. However, Brooker had used piperidine at a low temperature (Kodak Ltd., B.PP. 436,941/1933; 437,017/1933), and this method proved applicable here. By thus condensing 2-methylbenzthiazole ethiodide, with (I), (III), (IV), (II), and the crude (V), respectively, there resulted the β-methylthiatricarbocyanine (VI), which has been already described (I.G. Farbenind. A.-G., B.P. 394,537/1931), and



(VI.)

the corresponding γ- and δ-*methyl*-, and ββ′- and β*δ-dimethyl-thiatricarbocyanines*. By condensing 5 : 6-dimethoxy-2-methylbenzthiazole ethiodide and 2-methyl-6 : 7-benzbenzthiazole ethiodide, respectively, with (II), the 5 : 6 : 5′ : 6′-*tetramethoxy*- and 6 : 7 : 6′ : 7′-*dibenz*-derivatives of the ββ′-dimethylthiatricarbocyanine were prepared. The dye obtained by condensing 2-methyl-6 : 7-benzbenzthiazole ethiodide with (IV) has already been described (*idem, ibid.*). By condensing 2-methylbenzselenazole ethiodide with (II), (III), and (IV), respectively, there resulted a ββ′-*dimethyl*-, and a γ- and a δ-*methyl-selenatricarbocyanine*.

Condensation of (IV) and (V), respectively, with 2-methylthiazoline ethiodide gave the δ-*methylthiazolinocarbocyanine* (VII) and the corresponding βδ-*dimethyl* compound.



(VII.)

We compared the absorption maxima in methyl-alcoholic solution of the chain-substituted tricarbocyanines with the corresponding parent dyes : the figures are shown in the accompanying table. In one instance, introduction of a β-methyl group caused a bathochromic shift of 60 A. Introduction of a γ-methyl group caused a bathochromic shift of 5 A. and a hypsochromic shift

Chain.	Absorption (A.) of tricarbocyanine iodides : Thia-.	Tetramethoxythia-.	Dibenzthia-.	Selena-.	Thiazolino-.
Unsubstituted	7620 *	8000	7970 *	7700 *	6450 †
β-Me	7680	—	—	—	—
γ-Me	7610	—	—	7705	—
δ-Me	7900	—	8250	8000	6750
ββ′-Me_2	7720	7900	8290	7970	—
βδ-Me_2	7060	—	—	—	6585

* Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703.
† Fisher and Hamer, *J.*, 1933, 189.

of 10 A. Introduction of a δ-methyl group had a more profound effect; thus, in four instances this caused consistently a bathochromic shift, the values being 280, 280, 300, and 300 A. The introduction of ββ′-dimethyl groups caused a hypsochromic shift of 100 A. in one case, but bathochromic shifts, of 100, 320, and 270 A., respectively, in three others. βδ-Dimethyl groups produced a hypsochromic shift of 560 A. and a bathochromic shift of 135 A.

These chain-substituted tricarbocyanines comprise photographic sensitisers but, as already noted for symmetrical dicarbocyanines carrying a methyl group on the chain (Hamer and Rathbone, *J.*, 1945, 595), it cannot be said that they are in general better than the parent dyes with an unsubstituted chain.

Experimental.

1-*Anilino*-5-*anilo*-1-*methyl*-1 : 3-*pentadiene Hydrobromide* (I).—Cyanogen bromide (5 g.; 1 mol.) was added to water (30 c.c.) which was cooled with ice. Aniline (10 c.c.; >2 mols.) was added and α-picoline (5 c.c.; 1 mol.) was gradually stirred in. After 30 minutes in ice, the mixture was gradually treated with ice-cold hydrobromic acid (14 c.c., *d* 1·45; 2·5 mols.). After standing in the cold overnight, the red solid was filtered off and ground once with water (20 c.c.) and thrice with acetone (19% yield; 3·00 g.). This and the other pentadiene derivatives were dried in a vacuum desiccator before analysis (Found : Br, 23·25. $C_{18}H_{19}N_2Br$ requires Br, 23·3%). The maroon crystals had m. p. about 155° (decomp.), depending on the rate of heating. Their absorption maximum was at 4760 A. whereas the corresponding substance with an unsubstituted chain had its maximum at 4870 A. They sensitised a gelatino-bromide photographic emulsion weakly up to 5700 A.

1-*Anilino*-5-*anilo*-1 : 5-*dimethyl*-1 : 3-*pentadiene hydrochloride* (II) was similarly prepared from aniline (10 c.c.), cyanogen bromide in ice-cold water, and αγ-lutidine, followed by concentrated hydrochloric acid. The solid was filtered off, ground with water (40 c.c.) and thrice with acetone (40 c.c. × 2, 60 c.c.). The yield (7·28 g.) was 25% (Found : Cl, 11·3. $C_{19}H_{21}N_2Cl$ requires Cl, 11·3%). The red crystals had m. p. 150—151° (decomp.). The absorption maximum was at 4915 A. and the dye had no photographic sensitising action.

1-*Anilino*-5-*anilo*-2-*methyl*-1 : 3-*pentadiene hydrobromide* (III) was similarly prepared from cyanogen bromide (5 g.) in cold water with aniline and β-picoline, followed by hydrobromic acid. The yield of washed hydrobromide was 37% (Found : Br, 22·8. $C_{18}H_{19}N_2Br$ requires Br, 23·3%). The maroon crystals had m. p. about 148° but dependent on the rate of heating. The absorption maximum was at 4880 A. The dye did not sensitise. In another experiment more hydrobromic acid (another 2·5 mols.) was added and produced a pale pink solid. It was filtered off and washed with acetone (2·4 g. obtained; 9% yield) and appeared to be the *dihydrobromide*, m. p. 239° (decomp.) (Found : Br, 37·75. $C_{18}H_{20}N_2Br_2$ requires Br, 37·7%). The hydrochloride was similarly prepared.

1-*Anilino*-5-*anilo*-3-*methyl*-1 : 3-*pentadiene Hydrobromide* (IV).—To cyanogen bromide (5 g.; 1 mol.) in water (10 c.c.), with slight cooling, was added a mixture of γ-picoline (5 c.c.; 1 mol.) and aniline (10 c.c.; >2 mols.). A vigorous reaction occurred with rise of temperature. Hydrobromic acid was stirred in (14 c.c., *d* 1·45; 2·5 mols.), followed quickly by ice-water. The yield of washed solid was 6·65 g. (31%), and this was used in condensations. On recrystallising a sample from methyl alcohol (50 c.c. per g.) the yield was 13% (Found : Br, 23·2. $C_{18}H_{19}N_2Br$ requires Br, 23·3%). The dark maroon crystals had m. p. 167° (decomp.). The absorption maximum was at 4805 A. and there was no photographic sensitisation. When the reaction temperature was kept down by cooling with ice, the yield of dye was only 1%.

1-*Anilino*-5-*anilo*-1 : 3-*dimethyl*-1 : 3-*pentadiene Hydrobromide* (V).—A solution of aniline (10 c.c.; 2·2 mols.) and αγ-lutidine (5 c.c.; 1 mol.) in ether (20 c.c.) was added to a solution of cyanogen bromide

(5 g.; 1 mol.) in ether (10 c.c.), and the mixture warmed for 2 minutes. Hydrobromic acid (14 c.c., *d* 1·45; 2·5 mols.) was added. The ether-washed solid was obtained in 51% yield (8·08 g.), but tended to become oily on standing in the air. It was used as quickly as possible for dye condensations, being kept meanwhile in a vacuum desiccator.

Bis-2-(3-*ethylbenzthiazole*)-β-*methylheptamethincyanine Iodide* (VI).—2-Methylbenzthiazole ethiodide (3·05 g.; 2 mols.) and 1-anilino-5-anilo-1-methyl-1 : 3-pentadiene hydrobromide (I) (1·72 g.; 1 mol.) were added to ice-cold absolute alcohol (30 c.c.), and a cooled solution of piperidine (1·1 c.c.; 2·2 mols.) in alcohol (5 c.c.) was stirred in. After three days in the ice-chest, the solid was filtered off, washed with alcohol and with ether, and finally with warm water (40 c.c.), after which the yield was 65% (1·84 g.). After recrystallisation from methyl alcohol (650 c.c.), the yield was 33% (0·96 g.) and, after a second recrystallisation (450 c.c. per g.) in the presence of charcoal (0·75 g. per g.), it was 10%. For analysis it was dried to constant weight in a vacuum at 60—80° and this method of drying was applied to the subsequent dyes also (Found : I, 22·6. Calc. for $C_{36}H_{37}N_2IS_2$: I, 22·75%). The green crystals with a golden reflex had m. p. 215° (decomp.) (see B.P. 394,537/1931, example 6).

Bis-2-(3-*ethylbenzthiazole*)-γ-*methylheptamethincyanine Iodide*.—A similar preparation was carried out but with (III). The crude product (60% yield) was recrystallised from methyl alcohol (42 c.c. per g.), and gave dark green crystals, in 16% yield (Found : I, 22·8. $C_{27}H_{27}N_2IS_2$ requires I, 22·7%); m. p. 166° (decomp.). The sensitising maximum was at 8150 A.

Bis-2-(3-*ethylbenzthiazole*)-δ-*methylheptamethincyanine iodide* was similarly prepared but with (IV). The crude dye (76% yield) was recrystallised from methyl alcohol (425 c.c. per g.) and gave a 43% yield of light green crystals with a gold reflex (Found : I, 22·8. $C_{36}H_{37}N_2IS_2$ requires I, 22·75%); m. p. 206° (decomp.). Sensitisation extended from 7000 to 9000 A. with the maximum at 8300.

Bis-2-(3-*ethylbenzthiazole*)-ββ′-*dimethylheptamethincyanine iodide* was similarly prepared from 2-methylbenzthiazole ethiodide (2·94 g.) and (II). The product was ground with water (20 c.c.), and twice with acetone (20 c.c. × 2), boiled out twice with methyl alcohol (50 c.c. × 2), and recrystallised from methyl alcohol (1350 c.c.), the yield of green crystals then being 10% (0·27 g.) (Found : I, 22·5. $C_{37}H_{39}N_2IS_2$ requires I, 22·2%); m. p. 208° (decomp.). The sensitising maximum was at 8350 A.

Bis-2-(3-*ethylbenzthiazole*)-βδ-*dimethylheptamethincyanine Iodide*.—Starting from 2-methylbenzthiazole ethiodide (12·2 g.) and crude (V), the crude yield was only 2% (0·2 g.). After boiling out with absolute alcohol (5 c.c.) and recrystallisation from methyl alcohol (15 c.c.), it was less than 1% (0·08 g.) [Found (micro-analysis by Weiler and Strauss) : I, 22·6. $C_{37}H_{39}N_2IS_2$ requires I, 22·2%]. The bright green crystals had m. p. 155° (decomp.). Photographic sensitisation was from 7200 to 8500 with the maximum at 8200 A.

Bis-2-(5 : 6-*dimethoxy*-3-*ethylbenzthiazole*)-ββ′-*dimethylheptamethincyanine Iodide*.—5 : 6-Dimethoxy-2-methylbenzthiazole ethiodide (5·84 g.; 2 mols.), (II) (2·5 g.; 1 mol.), and absolute alcohol (40 c.c.) were stirred mechanically at 80°. A solution of piperidine (1·8 c.c.; 2·2 mols.) in alcohol (up to 12 c.c.) was added in 12 portions (1 c.c. per minute) and stirring was for 12 minutes. After cooling, the solid was filtered off, washed once with alcohol, twice with warm water (20 c.c. × 2), and repeatedly with acetone. The residue (0·27 g.; 5% yield) was recrystallised from methyl alcohol (500 c.c.), and the yield was 2% (Found : I, 18·3. $C_{31}H_{37}O_4N_2IS_2$ requires I, 18·3%). The green crystals had m. p. 210° (decomp.).

Bis-2-(3-*ethyl*-6 : 7-*benzbenzthiazole*)-ββ′-*dimethylheptamethincyanine Iodide*.—This was prepared from 2-methyl-6 : 7-benzbenzthiazole ethiodide (6·82 g.) and (II), with piperidine in ice-cold alcohol. The washed solid was boiled out with methyl alcohol (100 c.c.) and recrystallised from it (1000 c.c.), being obtained in 8% yield (0·51 g.) (Found : I, 19·2. $C_{35}H_{33}N_2IS_2$ requires I, 18·9%). The bronze crystals had m. p. 187° (decomp.). The sensitising maximum was at 8800 A. In the corresponding preparation carried out with 2-methyl-4 : 5-benzbenzthiazole ethiodide, the yield of tricarbocyanine was only 1%.

Bis-2-(3-*ethyl*-6 : 7-*benzbenzthiazole*)-δ-*methylheptamethincyanine Iodide*.—This was similarly prepared from 2-methyl-6 : 7-benzbenzthiazole ethiodide (3·55 g.) and (IV). The washed solid (1·02 g.) was boiled out with methyl alcohol (20 c.c.) and recrystallised from it (1100 c.c.). An 18% yield (0·6 g.) was obtained (Found : I, 19·15. Calc. for $C_{34}H_{31}N_2IS_2$: I, 19·3%). The bronze crystals had m. p. 187° (decomp.) (see B.P. 394,537/1931, example 8).

Bis-2-(3-*ethylbenzselenazole*)-ββ′-*dimethylheptamethincyanine Iodide*.—2-Methylbenzselenazole ethiodide (5·63 g.) was similarly allowed to react with (II). The washed solid was boiled out with methyl alcohol (70 c.c.), and recrystallised from it (1750 c.c.). The yield (0·97 g.) was 18% (Found : I, 19·3. $C_{37}H_{39}N_2ISe_2$ requires I, 19·4%). The green crystals had m. p. 214—217° (decomp.), the exact temperature depending on the rate of heating. The sensitising maximum was at 8450 A.

Bis-2-(3-*ethylbenzselenazole*)-γ-*methylheptamethincyanine iodide* was similarly prepared from 2-methylbenzselenazole ethiodide (7·71 g.) and (III). The washed product (3·17 g.) was boiled out with methyl alcohol (60 c.c.) and recrystallised from it (1000 c.c.), the yield being 18% (1·26 g.) (Found : I, 19·5. $C_{36}H_{37}N_2ISe_2$ requires I, 19·45%). The green crystals melted at 214° (decomp.). The sensitising maximum way at 8350 A.

Bis-2-(3-*ethylbenzselenazole*)-δ-*methylheptamethincyanine iodide* was similarly prepared from 2-methylbenzselenazole ethiodide (3·52 g.) and (IV). The washed solid (1·65 g.) was boiled out with methyl alcohol (30 c.c.) and recrystallised from it (1400 c.c.), being obtained in 30% yield (0·96 g.) (Found : I, 19·65. $C_{36}H_{37}N_2ISe_2$ requires I, 19·5%). It formed light green crystals with a golden reflex; m. p. 213° (decomp.). Sensitisation was from 7000 to 9000 A. with a maximum at 8400.

Bis-2-(3-*ethyl*-Δ^3-*thiazoline*)-δ-*methylheptamethincyanine Iodide* (VII).—This was prepared from 2-methylthiazoline ethiodide (5·14 g.) and (IV). The washed dye (3·85 g.) was recrystallised from methyl alcohol (25 c.c.), and the yield was 59% (2·65 g.) (Found : I, 27·5. $C_{18}H_{27}N_2IS_2$ requires I, 27·45%). It formed bluish-black crystals with a metallic lustre; m. p. 134° (decomp.). Sensitisation was from 6100 to 7500 A., with the maximum at 7100.

Bis-2-(3-*ethyl*-Δ^3-*thiazoline*)-ββδ-*dimethylheptamethincyanine Iodide*.—In a similar preparation carried out with (V), the yield of washed dye was only 5% and after recrystallisation from methyl alcohol (40 c.c. per g.) was 2% [Found (micro-analysis by Weiler and Strauss) : I, 26·8. $C_{19}H_{19}N_2IS_2$ requires

I, 26·65%]. The bluish-grey crystals had m. p. 165° (decomp.). The dye sensitised from 6000 to 7300 with the maximum at 6900 A.

We are indebted to Miss M. D. Gauntlett for the absorption measurements, and for the sensitising tests to Drs. B. H. Carroll, E. P. Davey, and E. B. Knott.

KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX. [*Received, October 29th*, 1946.]

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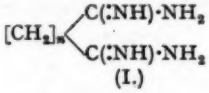
182. *Some Alkoxy- and Alkylenedioxydi-amines and Alkoxy- and Alkylenedioxydi-guanidines.*

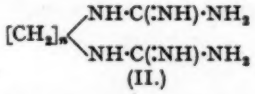
By A. T. FULLER and HAROLD KING.

The aim of the investigation was the preparation of a series of alkoxy- and alkylenedioxydi-amines (*O*-alkyl- and *OO'*-alkylene-hydroxylamines) and the corresponding alkoxy- and alkylenedioxydi-guanidines with a view to their being tested for antiprotozoal and antibacterial activity. Several representatives of all these types have been successfully made, starting from hydroxyurethane. Other methods of approach have been partly successful. Incidentally, two representatives of the hitherto undescribed class of *O*-alkoxydiguanides have been isolated.*

All these substances have been tested on a range of bacteria *in vitro*.

KING, LOURIE, and YORKE (*Lancet*, 1937, ii, 1360; *Ann. Trop. Med. Parasit.*, 1938, **32**, 177) discovered that diamidines (I), diguanidines (II), and di*iso*thioureas (III) had a pronounced trypanocidal action, some of the members where $n = 10$ or more being lethal to trypanosomes *in vitro* at a dilution of 1 in 250,000,000


(I.)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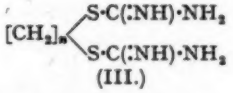
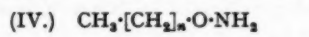

(III.)

Fuller (*Biochem. J.*, 1942, **36**, 548) examined the action of many of these bases, as salts, on a range of bacteria and found that their bacteriostatic titres were lower than their trypanocidal titres, but even so the activity was very pronounced in some of the higher members.

It seemed to us that in further exploration of the parent types the preparation of a series of alkoxyamines (IV), *N*-alkoxyguanidines (V), alkylenedioxydiamines (VI), and alkylenedioxydiguanidines (VII) might be worth undertaking.

(IV.) $CH_3 \cdot [CH_2]_n \cdot O \cdot NH_2$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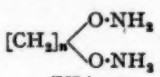
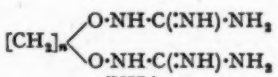
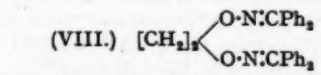
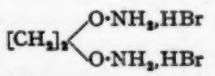

(VI.)


(VII.)

Direct alkylation of hydroxylamine leads to *N*-substitution, so for the preparation of *O*-substituted hydroxylamines, the amino-group must be partly or wholly protected. A number of ways of accomplishing this are described in the literature, but without preliminary exploration of these methods it was by no means certain which method would lend itself to the object we had in view.

Alkylation of oximes by methyl iodide or methyl sulphate leads, both with the aliphatic ketoximes (Dunstan and Goulding, *J.*, 1901, **79**, 628) and with the aromatic ketoximes (Semper and Lichtenstadt, *Ber.*, 1918, **51**, 928) to production of *O*- and *N*-methyl ethers. Borek and Clarke (*J. Amer. Chem. Soc.*, 1936, **58**, 2020) were, however, able to use acetoxime for the preparation of carboxymethoxyamine, $NH_2 \cdot O \cdot CH_2 \cdot CO_2H$ in 60% yield. On these lines a trial was made of the use of benzophenone oxime, which reacted in alcoholic solution with ethylene bromide and sodium ethoxide to give a single homogeneous *ethylenedibenzophenone oxime* of the probable constitution (VIII). The poor yield and slight dubiety about the structure led to the abandonment of this method of approach.

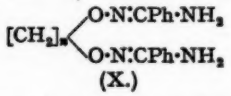
(VIII.) 

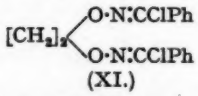

(IX.)

Luxmoore (*J.*, 1895, **67**, 1018) claimed to have prepared ethylenedioxydiamine dihydrobromide (IX) by the direct action of ethylene dibromide on hydroxylamine, but Werner and

* Curd and Rose (*J.*, 1946, 736) have, however, recently described the preparation of a member of this group of substances.

Gemeseus (*Ber.*, 1896, **29**, 1161) pointed out that Luxmoore's claim was inconsistent with the behaviour of hydroxylamine towards alkyl halides. These investigators were, however, able to prepare the corresponding dihydrochloride from the benzamidoxime ethylene ether (X, $n = 2$) of Falck (*Ber.*, 1886, **19**, 1481) which, on treatment with nitrite in the presence of hydrochloric acid, gave benzenyl chloride oxime ethylene ether (XI). The latter with sodium ethoxide furnished the ethylene ether of an ethylbenzhydroxamic acid (XII) which, without


(X.)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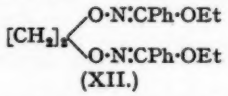
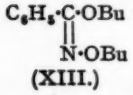

(XII.)

characterisation was hydrolysed to ethylenedioxydiamine. As this method seemed applicable to alkylenedioxydiamines, ethylene dibromide, 1 : 6-dibromohexane, and 1 : 12-dibromododecane have been condensed with benzamidoxime to give *ethylenedi*-OO′-*benzamidoxime dihydrochloride*, 1 : 6-*hexamethylenedi*-OO′-*benzamidoxime* (X, $n = 6$), and *dodecamethylenedi*-OO′-*benzamidoxime* (X, $n = 12$), respectively. In a similar way heptyl bromide was converted into O-*heptylbenzamidoxime* but all attempts to convert the latter or 1 : 6-hexamethylenedibenzamidoxime into the chloride oximes failed completely.

The success of Werner and Gemeseus in obtaining ethylenedioxydiamine, in unstated yield, depended essentially on a method for the preparation of the readily hydrolysable ethylene ether of ethylbenzhydroxamic acid (XII). To explore the possibility of a short route to allied compounds the direct butylation of benzhydroxamic acid was examined. When potassium benzhydroxamate was boiled with butyl bromide in alcohol in presence of potassium carbonate, equal weights of a non-acidic fraction and of an acidic fraction were obtained. The former, on fractional distillation, gave OO′-*dibutyl benzhydroximate* (XIII) as its main component and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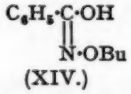
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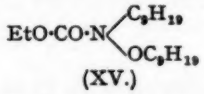
(XV.)

aniline, as a minor component, produced during the reaction by a Lossen rearrangement; (XIII) on hydrolysis with aqueous-alcoholic hydrogen chloride gave mainly ethyl benzoate and butoxyamine hydrochloride.

The acidic fraction on distillation proved to be O′-*butyl benzhydroxamate* (XIV) which on hydrolysis with hydrobromic acid gave *butoxyamine hydrobromide* and benzoic acid.

Whilst the foregoing method might prove suitable for the preparation of the alkoxyamines it would clearly lead to complications with alkylene dihalides.

Most of the above methods of approach to the synthesis of *O*-alkyl- and *OO′*-alkylenedihydroxylamines have involved compounds of oxime type where the nitrogen atom is doubly linked to carbon. Lauder W. Jones and his pupils (cf. Jones and Neuffer, *J. Amer. Chem. Soc.*, 1914, **36**, 2202) have successfully used hydroxyurethane, $OH{\cdot}NH{\cdot}CO_2Et$ for the preparation of the simplest *O*-alkylhydroxylamines. In our hands this method has proved capable of extension to the higher *O*-alkylhydroxylamines and to the *OO′*-alkylenedihydroxylamines. In the cases of the lower homologues up to heptyl no evidence was found for significant proportions of *N*-alkyl derivatives but from the products of the reaction between nonyl bromide and hydroxyurethane, *nonoxyurethane* and *nonoxynonylurethane* (XV) were obtained by fractional distillation. Similarly, alkylene dibromides have been found to give alkylenedioxydiurethanes except that with trimethylene and tetramethylene dibromides cyclisation took place with production of derivatives of *iso*oxazolidine and tetrahydro*iso*oxazine (King, *J.*, 1942, 432). For the hydrolysis of the urethanes, alkali and acid have been used successfully, but there is always some fission of ammonia.

All the hydroxylamines have been converted into alkoxyguanidines and alkylenedioxydiguanidines by use of *S*-methyl*iso*thiourea or cyanamide. Where cyanamide has been employed in excess, two representatives of the hitherto unknown *O*-alkoxydiguanides have been isolated as exemplified by *butoxydiguanide nitrate* and *hexoxydiguanide nitrate*. The former was also prepared by the action of dicyanodiamide on butoxyamine hydrochloride in boiling butyl alcohol. The parent substance hydroxydiguanide also seems to be unknown.

Finally, the complete methylation of heptoxyamine was attempted in methyl alcohol in the presence of potassium carbonate. The products were tetramethylammonium iodide and 2-*n*-heptylidene-*n*-heptaldehyde, identified as its *dinitrophenylhydrazone*:

$$C_7H_{16}ONH_2 \longrightarrow N(CH_3)_4I + CH_3{\cdot}[CH_2]_5{\cdot}CH{:}C(CHO){\cdot}[CH_2]_4{\cdot}CH_3$$

This reaction is fundamentally the same as that observed by Meisenheimer (*Annalen*, 1913, **397**, 273; cf. Jones and Major, *J. Amer. Chem. Soc.*, 1927, **49**, 1529), who found that evaporation of alcoholic solutions of ethoxy- and propoxy-trimethylammonium hydroxide led to production of acetaldehyde and propaldehyde respectively.

Antibacterial Activity.

The methods used were similar to those previously described (Fuller, *loc. cit.*). The results are summarised in the following table: the figures of inhibitory concentrations are those which prevented visible growth in 20 hours at 37° and are expressed as mg. per 100 c.c. (parts per 100,000). The sign > indicates that the drug was not active at the highest concentration tested.

	In blood.	In broth.				
	Strep. pyogenes.	*Strep. pyogenes.*	*Staph. aureus.*	*Cl. welchii.*	*E. coli.*	*B. proteus.*
Alkoxyamines (O-*Alkylhydroxylamines*).						
CH_3–	120	20	75	150	100	300
C_4H_9–	500	20	100	150	100	500
C_6H_{13}–	100	5	200	50	200	500
C_7H_{15}–	200	5	100	50	200	200
C_9H_{19}–	200	2	10	10	>20	>20
$C_{12}H_{25}$–	>5	1	>5	>5	>5	>5
Alkylenedioxydiamines (OO′-*Alkylenehydroxylamines*).						
–C_6H_{12}–	50	50	200	100	100	220
–$C_{10}H_{20}$–	100	1	100	8	>200	>200
Alkoxyguanidines.						
–C_4H_9	100	10	1000	50	1000	>1000
–C_6H_{13}	5	5	100	20	100	200
–C_7H_{15}	20	2	25	5	50	100
–C_9H_{19}	20	1	2	1·5	5	10
–$C_{12}H_{25}$	>10	0·2	0·8	1	2	5
Alkylenedioxydiguanidines.						
–C_6H_{12}–	50	10	200	200	>1000	>1000
–$C_{10}H_{20}$–	20	0·8	10	2	20	100

As is usual with basic drugs, these drugs are more active against the Gram-positive than the Gram-negative bacteria (*E. coli* and *B. proteus*). In a homologous series it is usual for activity to increase with chain length up to a point above which the activity decreases. The alkoxyguanidines, which are stronger bases than the *O*-alkylhydroxylamines, do not appear to have reached their maximum activity at C_{12}, while the *O*-alkylhydroxylamines show signs of having done so. This power of a more strongly basic group to support activity in a longer chain has been noted before (Fuller, *ibid.*).

The basicity of the compounds increases with the chain length. They are, however, such weak bases (the pH of their salts varies from pH 3 to pH 5·5) that none would be appreciably ionized at pH 7·5, so the observed differences of activity are probably not due to differences in their degrees of ionization.

The *O*-alkylhydroxylamines turned the colour of blood to brown or black, but the change was less marked with the alkoxyguanidines. Blood greatly reduced the activity of the drugs with increasing effect as the series was ascended, until the higher members retained 1% or less of the activity shown in broth.

Experimental.

Hydroxyurethane.—Hydroxylamine hydrochloride (27·8 g.; 1 mol.) was added to a solution of anhydrous sodium carbonate (62·4 g.; 1·5 mols.) in water (184 c.c.). The vigorously stirred solution, with salt in suspension, was slowly treated with ethyl chloroformate (42·4 g.), the temperature being kept approximately at that of the room. The final solution was acidified and extracted with ether in a continuous extractor. The yield of hydroxyurethane, dried over sodium sulphate, was about 94%. This method is based on Hantzsch's process (*Ber.*, 1894, **27**, 1255) and is more convenient than that of Jones (*Amer. Chem. J.*, 1898, **20**, 39).

Butoxyurethane and Butoxyamine Hydrochloride.—Hydroxyurethane (10·5 g.) and butyl iodide (18·4 g.) were added to ethyl alcohol (30 c.c.) containing dissolved potassium hydroxide (6·6 g., 85% pure) and the mixture boiled for 5 hours. The alcohol was removed, and the crude butoxyurethane recovered by ether extraction; yield 11·65 g. This urethane was boiled for one hour with potassium hydroxide (16·2 g.; 4 mols.) in water (32·4 c.c.). A solid potassium salt separated first but this quickly

disappeared and was followed by separation of an oily layer. The latter was taken up in ether, and the ethereal extract treated with slight excess of 3N-hydrochloric acid. This acid solution was evaporated to dryness, and the crystalline residue dissolved in boiling ethyl acetate. Butoxyamine hydrochloride, m. p. 156—157°, separated in glistening leaflets (5·3 g.) identical with the product obtained from the butylation of benzhydroxamic acid (see below).

Butoxyguanidine Nitrate.—Butoxyamine hydrochloride (9·3 g.) and cyanamide (6·3 g.) were boiled in absolute alcohol (50 c.c.) for six hours. The alcohol was removed, water added, and the required *nitrate* (9·8 g.) precipitated by adding excess of solid ammonium nitrate. It was twice crystallised from 1·5 vols. of water and separated in well-formed tablets, m. p. 77—78° (Found: C, 31·1; H, 7·5. $C_5H_{13}ON_3,HNO_3$ requires C, 30·9; H, 7·3%). On fractionation of the mother-liquors a by-product was obtained in small quantity which separated from water in nodules but from alcohol in clusters of feathery needles, m. p. 116—117°. This proved to be *butoxydiguanide nitrate* (Found: C, 30·9; H, 6·3; N, 34·8. $C_6H_{15}ON_5,HNO_3$ requires C, 30·5; H, 6·8; N, 35·6%). A specimen was synthesised for comparison by boiling butoxyamine hydrochloride and dicyanodiamide in butyl-alcoholic solution and conversion into the nitrate. On admixture of the above by-product with this substance there was no depression of m. p.

Hexoxyurethane.—Potassium hydroxide (16·8 g.) in boiling absolute alcohol (168 c.c.) was treated with a mixture of hydroxyurethane (31·5 g.) and hexyl bromide (49·5 g.), and the resulting solution boiled for 6 hours. After removal of potassium bromide by filtration the alcohol was distilled off, the residue dissolved in water, and the *hexoxyurethane* extracted by ether and fractionally distilled; b. p. 147—148°/16 mm.; yield 36·6 g. (Found: N, 7·3. $C_9H_{19}O_3N$ requires N, 7·4%).

Acid hydrolysis. The foregoing urethane (18 g.) was boiled for two hours with constant-boiling hydrobromic acid solution (40 c.c.). On cooling, an oily layer separated which soon crystallised. It was collected, well pressed, and then washed with a little light petroleum to remove an oil; yield 7·9 g. On crystallisation of the dried solid from ethyl acetate, *hexoxyamine hydrobromide* separated in pearly flakes, m. p. 141° (Found: C, 36·7; H, 8·2. $C_6H_{15}ON,HBr$ requires C, 36·4; H, 8·2%). The hydrobromic acid mother-liquor after extraction with ether to remove non-basic material, mainly hexyl bromide, was basified and again extracted with ether. In this way a small quantity (2 g.) of the *base* was obtained, b. p. 159°/750 mm. (Found: C, 61·7; H, 13·0; N, 11·9. $C_6H_{15}ON$ requires C, 61·5; H, 12·8; N, 12·0%).

Alkaline hydrolysis. The urethane (36·4 g.) was boiled with potassium hydroxide (43 g.; 4 mols.) in water (215 c.c.) for 3·5 hours. The oily layer was taken up in ether, and the ethereal extracts combined and extracted with 2N-hydrochloric acid (150 c.c.). The acid extract was evaporated to dryness with absolute alcohol, dissolved in a small volume of dry ethyl acetate, and kept at 0°.

Hexoxyamine hydrochloride separated in pearly scales, and a further quantity was obtained from the mother-liquor by addition of dry ether, total yield 20·4 g. The ethereal extract (above) was evaporated and gave unchanged urethane (5·8 g.). The hydrochloride is sparingly soluble in boiling ethyl acetate and melts at 150—151° (Found: C, 46·9; H, 10·6. $C_6H_{15}ON,HCl$ requires C, 46·9; H, 10·5%).

Hexoxyguanidine Nitrate.—(1) *From methylisothiourea.* Hexoxyamine (3·5 g.; 1 mol.) in alcohol (20 c.c.) was treated with methyl*iso*thiourea sulphate (4·2 g.), and the solution boiled gently for 1 hour and then evaporated to a small volume; on keeping, it deposited methyl*iso*thiourea sulphate (0·7 g.). The residue obtained on evaporation to dryness was dissolved in water, and excess of ammonium nitrate added. Crude *hexoxyguanidine nitrate* (4·7 g.) gradually crystallised. It separated from water on recrystallisation in tablets, m. p. 72—73° (Found: C, 38·2; H, 8·5; N, 24·8. $C_7H_{17}ON_3,HNO_3$ requires C, 37·8; H, 8·2; N, 25·2%).

(2) *From cyanamide.* Hexoxyamine hydrochloride (7·68 g.) and cyanamide (4·4 g.; 2 mols.) were boiled in alcohol (25 c.c.) for 6 hours. The solvent was removed, water added, and then excess of ammonium nitrate. The oil which separated gradually solidified and after a tedious fractional crystallisation from water gave hexoxyguanidine nitrate (4·1 g.), identical with the above, and *hexoxydiguanide nitrate* (0·6 g.), m. p. 115—116°, which separated from water or alcohol in tiny plates (Found: C, 36·8; H, 7·5; N, 31·8. $C_8H_{19}ON_5,HNO_3$ requires C, 36·3; H, 7·6; N, 31·8%).

O-*Hexylcholestenone Oxime.*—Equimolecular quantities (M/1000) of cholestenone and hexoxyamine were boiled in ethyl alcohol (5 c.c.) for an hour. The crystalline *oxime* which separated was recrystallised three times from ethyl alcohol and separated in plates, m. p. 70° (Found: C, 81·4; H, 11·8. $C_{33}H_{57}ON$ requires C, 81·9; H, 11·9%).

In a similar way O-*hexylcholestanone oxime*, m. p. 51°, was obtained, crystallising in flattened prisms from alcohol (Found: C, 81·9; H, 12·2. $C_{33}H_{59}ON$ requires C, 81·6; H, 12·3%).

Heptoxyurethane.—This was prepared in the same way as the lower homologue, the yield of product, b. p. 158°/20 mm., being 47% (Found: N, 6·8, 6·9. $C_{10}H_{21}O_3N$ requires N, 7·0%).

Heptoxyamine Hydrobromide.—This salt was prepared by acid hydrolysis as described for its lower homologue, the yield of *hydrobromide*, m. p. 142°, from 38·4 g. of heptoxyurethane being 34·5 g. On crystallisation from ethyl acetate it separated in plates, m. p. 143° (Found: C, 39·7; H, 8·8. $C_7H_{17}ON,HBr$ requires C, 39·6; H, 8·6%). The hydrobromic acid mother-liquors on extraction with ether gave heptyl bromide (1·8 g.), b. p. 170—180°/749 mm.; and after the mother-liquors had been made alkaline, ether extraction gave O-*heptoxyamine*, 0·9 g. This base was prepared in larger quantity from its salt and had b. p. 179°/761 mm. (Found: C, 64·7; H, 13·2. $C_7H_{17}ON$ requires C, 64·1; H, 13·1%).

Methylation of Heptoxyamine.—The amine (1·31 g.) and methyl iodide (3·1 c.c.) in methyl alcohol (25 c.c.) were boiled with anhydrous potassium carbonate (4·1 g.) for 3 hours. The solvent was removed, the residue treated with a little water and ether and filtered from some well-formed prisms (0·7 g.), which were crystallised from methyl alcohol (90 c.c.) and were unmelted at 360°. This substance proved to be tetramethylammonium iodide (picrate, m. p. 312° undepressed by an authentic specimen).

The ethereal extract of the aqueous liquor on distillation left an oil with a strong sweet odour with the reactions of an aldehyde. It readily gave a *dinitrophenylhydrazone*, red needles (0·1 g.), m. p. 129°, from alcohol. This on analysis proved to be derived from 2-*n*-heptylidene-*n*-heptaldehyde (Found: C, 61·6; H, 7·8; N, 14·5. $C_{20}H_{30}O_4N_4$ requires C, 61·5; H, 7·8; N, 14·4%).

Heptoxyguanidine Nitrate.—This salt was prepared in a similar way to the lower homologue, the yield of crude *nitrate* from 3·9 g. of heptoxyamine being 4 g. It crystallised from water in prisms, m. p. 72° (Found: C, 41·6; H, 8·6; N, 24·1. $C_8H_{19}ON_3,HNO_3$ requires C, 40·7; H, 8·5; N, 23·7%).

Heptoxy-3 : 5-dinitrobenzamide.—Heptoxyamine (1·31 g.) in pyridine (5 c.c.) was heated with 3 : 5-dinitrobenzoyl chloride (1 mol.) at 100° for 30 minutes. On cooling and adding excess of hydrochloric acid, the *product* crystallised (2·6 g.). It was purified by grinding with sodium bicarbonate solution and could then be crystallised from ether as pale yellow needles, m. p. 83—84° (Found: C, 52·1, 52·1; H, 6·0, 5·9; N, 12·7. $C_{14}H_{19}O_6N_3$ requires C, 51·7; H, 5·8; N, 12·9%).

Nonoxyurethane.—The crude alkylated urethane prepared in the usual manner from hydroxyurethane (8·4 g.) and nonyl bromide (16·5 g.) was fractionally distilled and gave *nonoxyurethane* (8·4 g.), b. p. 179°/20 mm. (Found: N, 6·1. $C_{12}H_{25}O_3N$ requires N, 6·1%), and a higher-boiling fraction of *nonoxynonylurethane* (3·0 g.), b. p. 189°/2 mm. (Found: N, 3·9. $C_{31}H_{63}O_3N$ requires N, 3·9%).

Nonoxyamine Hydrobromide.—The urethane (8·4 g.) was boiled with constant-boiling hydrobromic acid (25 c.c.) for 2 hours. On cooling, the oily layer which separated gradually crystallised. It was collected, washed with a little 48% hydrobromic acid, and finally with a few drops of ether; yield 5·3 g. It was crystallised from ethyl acetate (20 c.c.) and separated in flakes, m. p. 138°; yield 4·1 g. (Found: C, 44·2; H, 9·4. $C_9H_{21}ON,HBr$ requires C, 44·9; H, 9·2%). The hydrobromic acid mother-liquor on extraction with ether gave nonyl bromide (3·0 g.), b. p. 215—220°/756 mm.

Nonoxyamine Hydrochloride.—The urethane (33·2 g.) was boiled with 16% hydrochloric acid (100 c.c.) for 24 hours. The *hydrochloride* separated in needles (10·6 g.), m. p. 146—149° (Found: C, 55·2; H, 11·3; Cl, 18·4. $C_9H_{21}ON,HCl$ requires C, 55·6; H, 11·5; Cl, 18·2%).

Nonoxyguanidine Nitrate.—Nonoxyamine hydrochloride (3·9 g.) was dissolved in N-sodium hydroxide (20 c.c.), and methyl*iso*thiourea sulphate (2·78 g.) in alcohol (15 c.c.) added. After boiling gently for 1 hour, the solution was evaporated to dryness, the residue dissolved in absolute alcohol, and the sodium chloride removed. The solution was again evaporated to dryness, the residue dissolved in water, and ammonium nitrate added in excess. The *nitrate* was collected (4·8 g.) and crystallised from water, separating in needles, m. p. 61—62° (Found: N, 20·9. $C_{10}H_{23}ON_3,HNO_3$ requires N, 21·2%).

Dodecoxyurethane.—From lauryl bromide (37 g.) the crude urethane (39·0 g.) was obtained in the usual way. As it could not be distilled without some decomposition, it was hydrolysed without further purification.

Dodecoxyamine Hydrobromide.—The urethane (20 g.) was boiled with constant-boiling hydrobromic acid (40 c.c.) for 3 hours; on cooling, the oily upper layer crystallised. It was collected by filtration, well pressed, and then washed with ether to remove adhering oil. The *hydrobromide* (9·1 g.) was recrystallised from ethyl acetate, separating in pearly plates, m. p. 133° (Found: C, 51·0; H, 9·9. $C_{12}H_{27}ON,HBr$ requires C, 51·0; H, 10·0%). The hydrobromic acid filtrate was extracted with ether, and the extract on fractional distillation gave lauryl bromide (9·9 g.), b. p. 138—144°/18 mm.

Dodecoxyguanidine Nitrate.—The preceding hydrobromide (5·64 g.) was dissolved in N-sodium hydroxide solution (20 c.c.) and methyl*iso*thiourea sulphate (2·78 g.) in alcohol (15 c.c.) added. The reaction mixture was worked up as described for the corresponding nonyl derivative. The yield of crude *nitrate* was 4·1 g., and on crystallisation from water (100 c.c.) it separated in leaflets, m. p. 79° (Found: C, 50·9; H, 9·6; N, 18·0. $C_{13}H_{29}ON_3,HNO_3$ requires C, 50·9; H, 9·9; N, 18·3%).

1 : 6-*Hexamethylenedioxydiurethane.*—Hexamethylene dibromide (24·4 g.), hydroxyurethane (21 g.), and potassium hydroxide (11·2 g.) were boiled together in absolute alcohol (100 c.c.) for 6 hours. The alcohol was removed and an ethereal extract made of the residue when diluted by water. Removal of the ether left the crude urethane (28·7 g.), which could not be distilled at 1 mm. without decomposition.

1 : 6-*Hexamethylenedioxydiamine Dihydrochloride.*—The preceding urethane was boiled for 2·5 hours with potassium hydroxide (40 g.) in water (80 c.c.), during which period there was some evolution of ammonia. The oily layer was taken up in ether and distilled, the fraction, b. p. 90—120°/1 mm. (9·8 g.), being collected and redistilled, b. p. 112°/1 mm. (7·5 g.). It was treated with the calculated amount of N-hydrochloric acid, and the *dihydrochloride* was recrystallised twice from spirit. It separated in tiny leaflets, m. p. 220° (Found: C, 32·7; H, 8·1. $C_6H_{16}O_2N_2,2HCl$ requires C, 32·6; H, 8·2%).

Attempts to hydrolyse the urethane with constant-boiling hydrobromic acid or 16% hydrochloric acid gave very poor yields of base. For instance, the diurethane (14 g.) was boiled for 1·5 hours with 16% hydrochloric acid (50 c.c.) and gave a basic fraction (0·7 g.). A portion of this was converted into the *dipicrolonate* by mixing the calculated amounts of the components in alcohol. It was very sparingly soluble in boiling absolute alcohol and crystallised in minute needles, m. p. 229° (Found: C, 45·9; H, 4·7. $C_6H_{16}O_2N_2,2C_{10}H_8O_8N_4$ requires C, 46·4; H, 4·8%).

1 : 6-*Hexamethylenedioxydiguanidine Dinitrate.*—The preceding dihydrochloride (2·21 g.) was boiled in alcohol (20 c.c.) with cyanamide (1·68 g.) for 6 hours. The solvent was removed, and a small volume of water added, followed by excess of ammonium nitrate. An oil separated which eventually crystallised. It was collected, dried, and recrystallised from absolute alcohol or water, separating in pointed prisms, m. p. 123° (efferv.). The behaviour of the solid on heating in a capillary is variable: no melting takes place and the point of effervescence may occur at any temperature between 121° and 125° (Found: C, 27·2; H, 5·9; N, 30·7. $C_8H_{20}O_2N_8,2HNO_3$ requires C, 26·8; H, 6·2; N, 31·3%).

1 : 10-*Decamethylenedioxydiurethane.*—Dibromodecane (15 g.) and hydroxyurethane (10·5 g.) were boiled in absolute alcohol (60 c.c.) containing potassium hydroxide (5·6 g.) for 6 hours. The alcohol was removed by distillation and replaced by water, and the diurethane extracted with ether. On removal of the ether, the residue (15·9 g.) crystallised on cooling to 0°. A portion was crystallised from ether–light petroleum and gave the *urethane*, m. p. 53—55° (Found: C, 55·6; H, 9·3. $C_{16}H_{32}O_6N_2$ requires C, 55·1; H, 9·3%). Attempts to hydrolyse the main bulk of diurethane by acid were unsuccessful.

1 : 10-*Decamethylenedioxydiamine Dihydrochloride.*—The crude urethane from 15·0 g. of dibromodecane was boiled for 1 hour with potassium hydroxide (20·2 g.) in water (40·6 c.c.). A potassium salt separated at first but was soon replaced by an oily layer. During the hydrolysis some ammonia was given off. The oil was taken up in ether, the ether removed, and the residue distilled; yield 3·9 g.,

b. p. 144—145°/1 mm. The undistilled residue could be again hydrolysed to give a further quantity of base. The pure distilled base which readily solidified was converted into the *dihydrochloride* which could be crystallised from alcohol but preferably from 3N-hydrochloric acid, separating in tiny needles, m. p. 220° (Found : C, 43·1; H, 9·2. $C_{10}H_{24}O_2N_2,2HCl$ requires C, 43·3; H, 9·4%).

1 : 10-*Decamethylenedioxydiguanidine Dinitrate*.—The preceding dihydrochloride (1·4 g.) was boiled in alcoholic solution (10 c.c.) with cyanamide (0·84 g.) for 6 hours. The alcohol was removed, and the residue dissolved in water and treated with ammonium nitrate. The required *dinitrate* (2·2 g.) readily separated as a crystalline solid which was recrystallised from spirit (5 c.c.) and separated in rosettes of compact crystals, m. p. 135° (efferv.). The point of effervescence, like that observed for the corresponding hexamethylene derivative, is very variable, values as high as 147° being observed (Found : C, 35·1; H, 7·2; N, 26·5. $C_{12}H_{28}O_2N_6,2HNO_3$ requires C, 34·8; H, 7·3; N, 27·0%).

Butylation of Benzhydroxamic Acid.—Potassium benzhydroxamate (46·7 g.), spirit (225 c.c.), butyl bromide (41·1 g.), and excess of potassium carbonate were boiled for 15 hours, the alcohol removed by distillation, and the residue diluted with water and ether and filtered from unchanged potassium benzhydroxamate (5·6 g.). The combined ethereal extracts were treated with 7 successive portions of 2N-sodium hydroxide (98 c.c. in all) to remove acidic substances. The residual ethereal solution on evaporation left non-acidic substances (*A*, 23·6 g.). The alkaline extract on acidification and extraction with ether gave an acidic fraction (*B*, 23·9 g.).

Fraction (*A*), on fractional distillation, gave aniline (3·0 g.) and a main fraction (16·2 g.), b. p. 175—180°/13 mm., which on redistillation gave *OO'-dibutyl benzhydroximate*, b. p. 175—180°/13 mm. (Found : C, 72·2; N, 9·1; N, 5·5. $C_{15}H_{23}O_2N$ requires C, 72·3; H, 9·2; N, 5·6%). The dibutyl derivative was boiled with a mixture of absolute alcohol (100 c.c.) and hydrochloric acid (25 c.c., *d* 1·16) for 4 hours. The resultant solution was diluted with 2 vols. of water and extracted with ether. Washing of the latter with aqueous sodium bicarbonate removed benzoic acid (0·72 g.), and fractional distillation gave ethyl benzoate (8·35 g.), b. p. 213°, with no higher fraction. The main hydrochloric acid mother-liquor was evaporated to dryness under reduced pressure, finally with alcohol, and a small crop of ammonium chloride removed. On re-evaporation to dryness and solution in dry ether, butoxyamine hydrochloride separated as leaflets, m. p. 154°, undepressed by an authentic specimen (Found : Cl, 28·6. Calc. : Cl, 28·2%).

The acidic fraction (*B*), on distillation at 15 mm., had b. p. 182° and was much more viscous than the dibutyl compound; yield 17·0 g. Analysis showed it to be *O'-butyl benzhydroxamate* (Found : C, 68·1; H, 8·0; N, 7·6. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·2%). It was hydrolysed by boiling with constant-boiling hydrobromic acid for 6·5 hours. The solution was diluted with an equal volume of water, and ether extraction removed benzoic acid in quantitative yield. The hydrobromic acid solution was evaporated to small volume under reduced pressure with two additions of water, and the *butoxyamine hydrobromide* (4·8 g.) collected. It was crystallised from ethyl acetate and separated in pearly leaflets, m. p. 159—160° (Found : Br, 47·2. $C_4H_{11}ON,HBr$ requires Br, 47·0%). It was converted in aqueous solution by treatment with silver chloride into butoxyamine hydrochloride which, unlike the hydrobromide, is very sparingly soluble in boiling ethyl acetate. It crystallised in pearly leaflets, m. p. 156—157° (Found : Cl, 28·4. Calc. : Cl, 28·2%). Neuffer and Hoffman (*J. Amer. Chem. Soc.*, 1925, **47**, 1686) gave m. p. 152—153°.

O-*Heptylbenzamidoxime*.—Sodium (9·2 g.) was dissolved in absolute alcohol (150 c.c.) and, after addition of benzamidoxime hydrobromide (43·4 g.) and heptyl bromide (35·8 g.), was boiled for 6 hours. The alcohol was removed, and the residue treated with water and ether. The ethereal extract on distillation left a crystalline solid (42·7 g.) which distilled at 192°/11 mm. O-*Heptylbenzamidoxime* crystallised from ether in needles, m. p. 49—50° (Found : C, 71·9; H, 9·5. $C_{14}H_{22}ON_2$ requires C, 71·6; H, 9·5%). Attempts to convert this amidoxime into benzenyl chloride oxime *O*-heptyl ether by the action of nitrite in hydrochloric acid solution were unsuccessful. The amidoxime forms a sparingly soluble, oily hydrochloride which is not attacked by the nitrite, and an attempt to circumvent this by carrying out the reaction in glacial acetic acid with amyl nitrite and hydrochloric acid was also unsuccessful.

Ethylenedi-O-*benzamidoxime Dihydrochloride*.—Ethylene bromide (4·7 g.), benzamidoxime (6·8 g.), and absolute alcohol (20 c.c., which had reacted with sodium, 1·2 g.) were boiled together for 4 hours. The alcohol was removed by distillation, and the residue dissolved in water and made alkaline by addition of excess of 2N-sodium hydroxide solution. The solid which separated was dissolved in 3N-hydrochloric acid and readily crystallised in needles; yield 1·1 g., m. p. 234—235° (Found : C, 51·8; H, 5·7. $C_{16}H_{18}O_2N_4,2HCl$ requires C, 51·7; H, 5·4%). The hydrochloric acid mother-liquor on basification gave a further 0·25 g., m. p. 161°, of ethylenedibenzamidoxime base. No yields for this reaction are quoted by Falck (*Ber.*, 1886, **19**, 1485) or by Werner and Gemeseus (*ibid.*, 1896, **29**, 1162).

1 : 6-*Hexamethylenedi*-O-*benzamidoxime*.—Sodium (4·6 g.) was dissolved in absolute alcohol (100 c.c.), and benzamidoxime hydrobromide (21·7 g.), dissolved in warm absolute alcohol (20 c.c.), was added; a sodium salt separated. Hexamethylene bromide (12·15 g.) was then added, and the solution boiled for 6 hours. The alcohol was removed, and the residue treated with water. *Hexamethylenedibenzamidoxime* separated as an oil which soon solidified (14·7 g.). When crystallised from 70% alcohol and then from absolute alcohol it had m. p. 106° (Found : C, 67·2; H, 7·6; N, 15·5. $C_{20}H_{26}O_2N_4$ requires C, 67·7; H, 7·4; N, 15·8%). Attempts to convert this substance into hexamethylenedi-*O*-benzenyl chloride oxime were not successful.

1 : 12-*Dodecamethylenedi*-O-*benzamidoxime*.—Sodium (8·2 g.) was dissolved in absolute alcohol (250 c.c.), and benzamidoxime (21·7 g.) and dodecamethylene bromide (16·35 g.) added. The solution was boiled for 4 hours, the alcohol removed by distillation, and the residue made alkaline with N-sodium hydroxide solution. The oil which separated rapidly crystallised; yield 18 g. The crude *oxime* was very soluble in methyl alcohol but could best be crystallised from this solvent. It separated in broad short needles, m. p. 105—106° (Found : C, 71·4; H, 8·6. $C_{26}H_{38}O_2N_4$ requires C, 71·2; H, 8·7%). With 3N-hydrochloric acid it forms an oily hydrochloride.

Ethylenedi-O-*benzophenone Oxime*.—Benzophenone oxime (9·85 g.) and ethylene bromide (4·7 g.) were added to sodium ethoxide solution prepared from absolute alcohol (25 c.c.) and sodium (1·15 g.).

On boiling, sodium bromide rapidly separated; heating was continued for 6 hours. When cold, the sodium bromide and admixed needles were collected and the former removed by water, leaving the *oxime* (1·7 g.), which crystallised from absolute alcohol (60 c.c.) in pearly leaflets, m. p. 123—124° (Found: C, 80·3; H, 5·4; N, 6·4. $C_{13}H_{11}O_2N_3$ requires C, 80·0; H, 5·6; N, 6·7%). There was no evidence for the presence of any isomeric ether, the alcoholic mother-liquors giving only unchanged benzophenone oxime.

Preparation of Benzamidoxime Hydrobromide. Isolation of 2 : 4-*Diphenyl*-1 : 3 : 5-*oxadiazole.*—Phenyl cyanide (103 g.), hydroxylamine hydrochloride (69·5 g.), and anhydrous sodium carbonate (53 g.) were treated with water (150 c.c.), and ethyl alcohol added until the solution was homogeneous. The solution was boiled for 18 hours, the alcohol removed by distillation, and the aqueous residue extracted with ether. The ethereal extract was shaken with 24% aqueous hydrobromic acid (400 c.c.), and the latter on concentration gave a 76% yield of *benzamidoxime hydrobromide*, crystallising in prisms, m. p. 183° (Found: C, 39·0; H, 4·7. $C_7H_8ON_2,HBr$ requires C, 38·7; H, 4·2%). The ethereal solution on fractional distillation gave phenyl cyanide (9·5 g.) and a non-volatile crystalline residue (2·35 g.). The latter on crystallisation from methyl alcohol separated in long silky needles, m. p. 107°, which proved to be 2 : 4-diphenyl-1 : 3 : 5-oxadiazole (Found: C, 75·4; H, 4·8. Calc. for $C_{14}H_{10}ON_2$: C, 75·7; H, 4·5%). The final hydrobromic acid mother-liquor contained benzamide (4·0 g.).

Wolf (*Ber.*, 1898, **31**, 2111) gives m. p. 168° for benzamidoxime hydrochloride. In our hands this salt crystallised from alcohol and ether in stout prisms, m. p. 203° (Found: C, 48·9; H, 5·3; Cl, 20·5. Calc. for $C_7H_8ON_2,HCl$: C, 48·7; H, 5·3; Cl, 20·5%).

Our thanks are due to Mr. E. V. Wright for able assistance in the experimental work.

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183. 3-*Deoxy*-l-*xylose.*

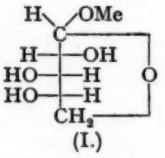
By S. Mukherjee and A. R. Todd.

In the course of experiments initiated in search of new synthetic routes to 2-deoxyribose derivatives, 2 : 3-*anhydro*-β-*methyl*-l-*ribopyranoside*, prepared from β-methyl-*l*-arabopyranoside, has been treated with sodium thiomethoxide and the product refluxed in alcohol with Raney nickel. The product was 3-*deoxy*-β-*methyl*-l-*xylopyranoside* containing at most only traces of a 2-deoxypentoside. Acid hydrolysis gave 3-*deoxy*-l-*xylose* as a syrup, characterised as its *p*-*nitrophenylosazone*, and yielding on oxidation *l*-*erythro*-1 : 3 : 4-trihydroxyvaleric acid isolated as its phenylhydrazide. Hydrogenolysis of the same anhydro-glycoside gave mainly 3-deoxy-β-methyl-*l*-xylopyranoside, apparently accompanied by a small amount of a 2-deoxypentoside, since the product showed a small uptake of oxidant on titration with periodate. 2 : 3-*Anhydro*-α-*methyl*-l-*ribopyranoside* treated in similar fashion with sodium thiomethoxide, followed by refluxing in alcohol with Raney nickel, also gave a product whose major constituent was 3-deoxy-α-methyl-*l*-xylopyranoside, since the syrupy sugar obtained from it by hydrolysis yielded 3-deoxy-*l*-xylose *p*-nitrophenylosazone on warming with *p*-nitrophenylhydrazine.

The work described in this paper was undertaken in connection with studies on the synthesis of purine and pyrimidine nucleosides in progress in this laboratory, and which required for extension to the deoxyribonucleosides considerable quantities of 2-deoxy-*d*-ribose. 2-Deoxy-*l*-ribose has been prepared from *l*-arabinose (Levene and Mori, *J. Biol. Chem.*, 1929, **83**, 803; Levene, Mikeska, and Mori, *ibid.*, 1930, **85**, 785) using the standard glycal route first developed by Fischer (*Ber.*, 1914, **47**, 196), but the exploration of other routes which might give better yields of 2-deoxyribose derivatives seemed desirable. The use of 2 : 3-anhydro-sugar derivatives as intermediates in the synthesis of deoxy-hexoses has recently been described by Prins, Reichstein, and their co-workers who have prepared in this way various derivatives of 3-deoxy-*d*-glucose (Prins, *Helv. Chim. Acta*, 1946, **29**, 1), 2-deoxy-*d*-allose (Jeanloz, Prins, and Reichstein, *ibid.*, p. 371), cymarose (Prins, *ibid.*, p. 378) and 3-deoxy-*l*-mannose (Bollinger and Prins, *ibid.*, p. 1061). Following a discussion with the Swiss workers it was agreed that we should seek to apply similar methods in the pentose series in the hope that they would lead to a preparative method for 2-deoxyribose derivatives. For convenience we first carried out the proposed sequence of reactions starting with *l*-arabinose, which was expected to yield finally either 2-deoxy-*l*-ribose or 3-deoxy-*l*-xylose or possibly a mixture of both. In fact, it was found that 3-deoxy-*l*-xylose was formed as the main product; no 2-deoxy-*l*-ribose derivative could be isolated, although there was some evidence that traces of 2-deoxy-derivatives were formed.

β-Methyl-*l*-arabopyranoside (I) condensed with acetone to give an acetone derivative whose formulation as 3 : 4-iso*propylidene* β-*methyl*-l-*arabopyranoside* (II) follows from the transformations described below. Treatment of (II) with *p*-toluenesulphonyl chloride in pyridine yielded 2-p-*tosyl* 3 : 4-iso*propylidene* β-*methyl*-l-*arabopyranoside* (III) hydrolysed to 2-p-*tosyl* β-*methyl*-l-*arabopyranoside* (IV). The location of the tosyl group in (IV), and hence the structures

allotted to (II) and (III), are confirmed by the fact that on titration of (IV) with periodate 1 mol. of oxidant is consumed. Cold methanolic sodium methoxide converted (IV) into a crystalline anhydro-compound formulated from its mode of preparation as 2 : 3-*anhydro*-β-*methyl*-l-*ribopyranoside* (V) which, warmed with methanolic sodium thiomethoxide, yielded a syrupy sulphur-containing glycoside. Assuming a *trans*-opening of the ethylene oxide ring of (V) with inversion at the carbon atom to which the sulphur attaches itself this product might have been 3-*methylthio* β-*methyl*-l-*xylopyranoside* (VI), 2-methylthio β-methyl-*l*-arabopyranoside, or a mixture of both. Although from the experience of Jeanloz, Prins, and Reichstein (*loc. cit.*) in the *d*-allose series production of the 2-methylthio-product in reasonable amount might have been expected, subsequent reactions show that our product consisted almost entirely of (VI), the 2-methylthio-compound being present at most in traces. The syrupy methylthio-compound was refluxed in alcoholic solution with Raney nickel, prepared according to Mozingo *et al.* (*J. Amer. Chem. Soc.*, 1943, **65**, 1013); it then yielded a sulphur-free glycoside which was stable to periodate, the uptake of oxidant on titration being within the limits of experimental error. This product we regard as 3-*deoxy*-β-*methyl*-l-*xylopyranoside* (VII). The possibility that it was contaminated by a trace of 2-deoxy-β-methyl-*l*-riboside cannot be excluded since it could not be crystallised and it gave a feeble green colouration in the Keller–Kiliani test commonly regarded as specific for 2-deoxy-sugars. Acid hydrolysis of (VII) yielded the free 3-*deoxy*-l-*xylose* (VIII) as a syrup yielding a crystalline p-*nitrophenylosazone*. The structure allotted to (VIII) was confirmed by oxidation with bromine water, lactonisation of the acid produced, and conversion into a crystalline phenylhydrazide, which agreed in m. p., analysis, and, within the limits of error, optical rotation with *l*(+)-*erythro*-1 : 3 : 4-trihydroxyvaleric acid phenylhydrazide (IX) prepared by Nef (*Annalen*, 1910, **376**, 48), who on the basis of its dextrorotation described it as the *d*-*erythro*-compound.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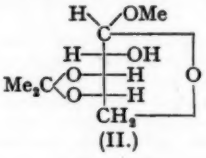
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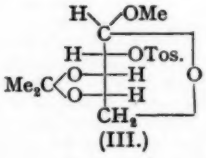
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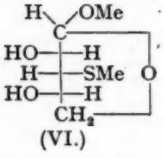
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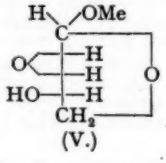
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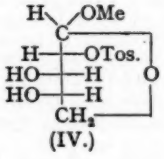
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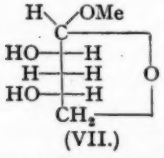
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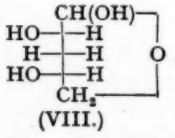
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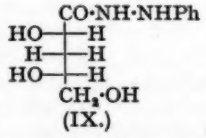
(IX.)

As an alternative route the ethylene oxide ring in (V) was opened by hydrogenolysis under pressure using a nickel catalyst. The syrupy product produced was again mainly (VII) but there was more evidence of the presence of an appreciable amount of a 2-deoxy-pentose derivative, since the green colour produced in the Keller–Kiliani test, although weak, was stronger than in the case of the product obtained *via* the methylthio-glycoside, and on periodate titration 0·17 mol. of oxidant was consumed. On acid hydrolysis followed by treatment of the syrupy free sugar with *p*-nitrophenylhydrazine, however, only the *p*-nitrophenylosazone of 3-deoxy-*l*-xylose could be isolated. No further attempts were made to isolate any 2-deoxy-pentose present, since it was evident that even if they were successful the method would hardly be of preparative value.

In the preparation of β-methyl-*l*-arabopyranoside a considerable amount of a syrupy mixture of the α- and the β-isomer was left after removal of the crystalline β-compound. This syrup was condensed with acetone and the product tosylated. After separation of a quantity of the crystalline 2-*p*-tosyl 3 : 4-*iso*propylidene β-methyl-*l*-arabopyranoside the residual syrup was subjected to mild hydrolysis; from the resulting syrup 2-p-*tosyl* α-*methyl*-l-*arabopyranoside* was isolated. By methods exactly analogous to those used above in the β-series this compound

was converted into 2 : 3-*anhydro*-α-*methyl*-l-*ribopyranoside*, the latter reacted with sodium thiomethoxide, and the product treated with Raney nickel. The resulting syrup gave analytical values corresponding to a deoxy-methylpentoside, and from the fact that it consumed *ca.* 0·3 mol./mol. of periodate on titration it appeared to be a mixture of (VII) with a smaller amount of a 2-deoxy-compound; on hydrolysis and treatment of the product with *p*-nitrophenylhydrazine only 3-deoxy-*l*-xylose *p*-nitrophenylosazone was isolated. This was rather surprising in view of the periodate titration value mentioned above, but it is possible that this value may give an exaggerated estimate of the content of 2-deoxy-pentoside in the mixture.

The results obtained indicate that the projected route to 2-deoxyribose from arabinose *via* the 2 : 3-anhydroarabinosides is unlikely to be of any practical interest if, indeed, it can be realised. The route, however, does form a fairly convenient method for the preparation of 3-deoxy-*l*-xylose and its derivatives, since the overall yield from methyl-*l*-arabopyranoside is very satisfactory. Other possible routes to 2-deoxyribose derivatives are under investigation and will be reported upon in due course.

Experimental.

β-Methyl-l-arabopyranoside.—Following the procedure of Hudson (*J. Amer. Chem. Soc.*, 1925, **47**, 267) we obtained from *l*-arabinose (100 g.) pure β-methyl-*l*-arabopyranoside (32 g.), together with a syrupy mixture of the α- and the β-isomer (*ca.* 75 g.).

3 : 4-iso*Propylidene β-Methyl-l-arabopyranoside.*—To an ice-cold suspension of finely powdered β-methyl-*l*-arabopyranoside (32 g.) in dry acetone (750 c.c.), phosphoric oxide (26 g.) was gradually added with stirring. The temperature was kept below 5° and stirring continued until the starting material dissolved (*ca.* 3 hours), then set aside overnight in the refrigerator. The supernatant liquid was decanted from the mixture of phosphoric acid, etc., which had settled to the bottom of the flask, and neutralised by gradually adding concentrated aqueous potassium hydroxide. The mixture was filtered and the filtrate concentrated under reduced pressure (bath temp. 35°). The syrupy product was distilled at 80—90° (bath temp.)/5 × 10^{-4} mm. giving the iso*propylidene* derivative as a colourless syrup (29 g.; 72·5%). $[\alpha]_D^{20°}$ +175·7°±0·5° (*c*, 5·2 in chloroform) (Found: C, 53·3; H, 7·7. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8%). The same product was obtained although in much lower yield by carrying out the condensation of β-methyl-*l*-arabopyranoside with acetone in presence of anhydrous copper sulphate and sulphuric acid.

2-p-*Tosyl* 3 : 4-iso*Propylidene β-Methyl-l-arabopyranoside.*—*p*-Tosyl chloride (28·5 g.) was added to a solution of 3 : 4-*iso*propylidene β-methyl-*l*-arabopyranoside (27·3 g.) in dry pyridine (136 c.c.) and the mixture warmed at 40° for 24 hrs. A small amount of water (1 c.c.) was added, and the solution set aside at 0° for 30 minutes. More water (*ca.* 100 c.c.) and chloroform (*ca.* 250 c.c.) were added and the mixture was shaken. The chloroform layer was separated, and the aqueous layer extracted several times with small quantities of chloroform. The combined chloroform extracts were washed successively with ice-cold dilute sulphuric acid, sodium hydroxide, and water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue recrystallised from alcohol gave colourless rod-shaped prisms (37·5 g.), m. p. 133°, $[\alpha]_D^{18°}$ +187·3°±2° (*c*, 1·55 in chloroform) (Found: C, 53·8; H, 6·1; S, 8·6. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·2; S, 8·9%).

2-p-*Tosyl β-Methyl-l-arabopyranoside.*—A solution of 2-p-*tosyl* 3 : 4-iso*propylidene β-methyl-l-arabopyranoside* (34 g.) in a mixture of methanol (1400 c.c.) and dilute sulphuric acid (280 c.c. of N) was heated at 40° for 4 hours; a further quantity of sulphuric acid (280 c.c. of N) was then added and the solution maintained at 40° for a further 4 hours, then cooled and neutralised by shaking with precipitated barium carbonate. Filtration followed by removal of solvents under reduced pressure (bath temp. 40°) gave a syrup which was taken up in ether; the solution was dried (Na_2SO_4) and evaporated. The residue solidified on removal of the last traces of solvent in a vacuum. The product (30 g.) could be purified by precipitation from ethereal solution with pentane; it then had m. p. *ca.* 43°, but was very hygroscopic. $[\alpha]_D^{20°}$ +115°±1° (*c*, 3·47 in chloroform) (Found: C, 49·1; H, 5·9. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7%).

2 : 3-*Anhydro-β-methyl-l-ribopyranoside.*—Ice-cold methanolic sodium methoxide (75 c.c. of a solution prepared by dissolving 6 g. sodium in 100 c.c. methanol) was added to a solution of 2-p-*tosyl β-methyl-l-arabopyranoside* (28·2 g.) in chloroform (350 c.c.) at 0°, and the mixture set aside in the refrigerator for 3 days with occasional shaking, then left at room temperature for a further 24 hours and neutralised with N-sulphuric acid. The chloroform layer was separated and the aqueous layer extracted with chloroform, and the combined chloroform extracts were dried (Na_2SO_4) and evaporated under slightly reduced pressure (bath temp. 40°). The *anhydro-glycoside* was obtained as a colourless syrup (11·4 g.), which on being kept in a desiccator over phosphoric oxide slowly set to a mass of needles which were so hygroscopic that a satisfactory m. p. determination could not be made. $[\alpha]_D^{18°}$ +35·7°±1° (*c*, 2·7 in chloroform) (Found: C, 49·3; H, 6·9. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

3-*Methylthio β-Methyl-l-xylopyranoside.*—2 : 3-Anhydro-β-methyl-*l*-ribopyranoside (5 g.) was dissolved in methanolic sodium thiomethoxide (37·5 c.c. containing 1·87 g. of sodium and 5 g. of methylthiol) and the solution refluxed for 2 hours, then cooled, exactly neutralised with N-sulphuric acid, and evaporated to dryness under reduced pressure (bath temp. 40°). The residue was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The brownish syrup (6·9 g.) could be purified by chromatography on active alumina in benzene solution; a small amount of material passed through the column, and elution of the adsorbed material with methanol gave the *product* (0·8 g. from 1 g.) as a faintly yellow syrup (Found: C, 43·2; H, 7·2. $C_7H_{14}O_4S$ requires C, 43·3; H, 7·3%).

3-*Deoxy-β-methyl-l-xylopyranoside.*—(1) *From* 3-*methylthio β-methyl-l-ribopyranoside.* The crude methylthio-compound (6 g.) was dissolved in a mixture of alcohol (300 c.c.) and water (70 c.c.), and

Raney nickel (150 g. prepared according to Mozingo *et al.*, *loc. cit.*) added. The mixture was heated under reflux for 2 hours and filtered, the nickel being thoroughly washed with alcohol, and the combined filtrate and washings were evaporated under reduced pressure. The residue was dissolved in water (35 c.c.), the solution thrice extracted with chloroform, and the aqueous phase evaporated under reduced pressure (bath temp. 40°) to a syrup, which was dissolved in acetone (30 c.c.) and filtered from inorganic material, and the acetone again evaporated under reduced pressure. The residue so obtained distilled at 110° (bath temp.)/4×10^{-3} mm. as a colourless hygroscopic syrup (3·6 g.). $[\alpha]_D^{18°}$ +142·2°±5° (*c*, 2·25 in chloroform) (Found: C, 48·0; H, 8·5. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2%). The *product* was virtually unaffected by sodium metaperiodate (0·2163 g. consumed 0·02 c.c. of M-periodate in 24 hours; 0·07 c.c. in 48 hours) but it gave a feeble green coloration in the Keller–Kiliani test.

(2) *From* 2 : 3-*anhydro*-β-*methyl*-l-*ribopyranoside*. Raney nickel (4 g.) was added to the anhydro-compound (3·3 g.) dissolved in alcohol (60 c.c.) and the mixture hydrogenated at 110°/100 atm. during 24 hours. Catalyst was removed by filtration and the filtrate evaporated under reduced pressure, yielding a colourless syrup which distilled at 100—105° (bath temp.)/10^{-3} mm. The product (2·2 g.) had $[\alpha]_D^{19°}$ +143°±4° (*c*, 2·868 in chloroform) (Found: C, 48·7; H, 8·3; OMe, 19·9. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2; OMe, 20·9). It gave a weak colour in the Keller–Kiliani test, and on titration with periodate it took up 0·17 mol. of reagent in 48 hours, suggesting that it may have been contaminated with some of the corresponding 2-deoxy-riboside.

3-*Deoxy*-l-*xylose*.—The syrupy glucoside obtained by method (1) above (0·3868 g.) was heated to 100° with dilute sulphuric acid (25 c.c. of 0·5N) until a constant rotation was attained (75 minutes). Specific rotations: after 60 minutes, +8·4°; after 75 minutes, +7·9°±1·5° (constant). The solution was neutralised with freshly precipitated barium carbonate, filtered, and evaporated under reduced pressure. The residual syrup was evaporated once under reduced pressure with methanol and dissolved in absolute alcohol. Inorganic matter was precipitated by addition of ether and the solution evaporated under reduced pressure yielding the *sugar* as a colourless syrup which immediately reduced Fehling's solution but could not be crystallised (Found: C, 44·4; H, 7·7. $C_5H_{10}O_4$ requires C, 44·8; H, 7·5%). Calculated from the final rotation of the hydrolysis solution the sugar had $[\alpha]_D^{18°}$ +8·7°±1·5°.

A similar product was obtained by hydrolysing a sample of 3-deoxy-β-methyl-*l*-xylopyranoside prepared by method (2) above; the specific rotation became constant after 90 minutes at +9°.

3-*Deoxy*-l-*xylose* p-*Nitrophenylosazone*.—This was prepared by heating 3-deoxy-*l*-xylose (230 mg. prepared *via* the methylthio-compound) in water (6 c.c.) with *p*-nitrophenylhydrazine (600 mg.) in glacial acetic acid (1 c.c.) for 1 hour on the steam-bath, and recrystallised from alcohol; dark red microcrystalline powder, m. p. 254—256° (Found: C, 51·2; H, 4·8; N, 20·9. $C_{17}H_{18}O_6N_6$ requires C, 50·7; H, 4·5; N, 20·9%). Similar treatment of a sample of the sugar prepared by the procedure involving hydrogenolysis of the anhydro-compound gave the same product; no other product could be isolated, although the m. p. of the crude *osazone* was somewhat lower.

l-erythro-1 : 3 : 4-*Trihydroxyvaleric Acid Phenylhydrazide*.—Bromine (0·25 c.c.) was added to a solution of 3-deoxy-*l*-xylose (470 mg.) in water (6 c.c.) and the mixture shaken in a closed vessel for 48 hours in the dark. Unchanged bromine was then removed under reduced pressure in a stream of air, the solution neutralised with freshly precipitated silver carbonate, and excess of silver removed with hydrogen sulphide. The solution obtained by filtering through charcoal was evaporated under reduced pressure and the residue evaporated once with methanol. The syrup (370 mg.) so obtained was lactonised by distillation at 120° (bath temp.)/3×10^{-4} mm. and the syrupy lactone (114 mg.) heated for 30 minutes at 100° with phenylhydrazine (100 c.mm.). After 3 hours a semi-crystalline mass had separated; ether was added and the colourless crystalline precipitate filtered off. Recrystallised from alcohol the hydrazide formed colourless needles, m. p. 149°, $[\alpha]_D^{18°}$ +4·5°±5° (*c*, 0·4 in alcohol) (Found: N, 11·7. Calc. for $C_{11}H_{16}O_4N_2$: N, 11·7%). Nef (*loc. cit.*) records for *d-erythro*-1 : 3 : 4-trihydroxyvaleric acid phenylhydrazide, m. p. 150° and $[\alpha]_D^{20°}$ +9·4°.

2-p-*Tosyl* α-*Methyl*-l-*arabopyranoside*.—The syrupy residue remaining after removing the crystalline β-methyl-*l*-arabopyranoside from the glycosidisation mixture from 100 g. of *l*-arabinose was condensed with acetone (1700 c.c.) in presence of phosphoric oxide (60 g.) as described above for the pure β-compound. The product (40 g.), a mixture of the α- and the β-isomer of 3 : 4-*iso*propylidene methyl-*l*-arabopyranoside, distilled at 100—110° (bath temp.)/10^{-3} mm. (Found: C, 52·8; H, 8·0. Calc. for $C_9H_{16}O_5$: C, 52·9; H, 7·8%).

The above α–β-mixture (40 g.) was dissolved in pyridine (200 c.c.) and tosylated as described under the β-compound. The product, a colourless syrup, was dissolved in a minimum amount of alcohol and set aside overnight in the refrigerator. Pure 2-*p*-tosyl 3 : 4-*iso*propylidene β-methyl-*l*-arabopyranoside (17·5 g.) separated, m. p. and mixed m. p. 133°. The alcoholic mother liquor gave on evaporation a syrup (42 g.) which was hydrolysed for 8 hours with methanol (1600 c.c.) and dilute sulphuric acid (650 c.c. of N). The hydrolysis solution was neutralised with precipitated barium carbonate, filtered, and evaporated under reduced pressure giving a syrup containing some crystalline material. This product was dissolved in ether, dried (Na_2SO_4), concentrated to *ca.* 250 c.c., and set aside overnight in the refrigerator. 2-p-*Tosyl* α-*methyl*-l-*arabopyranoside* separated as colourless needles (5·3 g.), m. p. 129—130°, $[\alpha]_D^{20°}$ −15·4°±0·4° (*c*, 4·88 in chloroform) (Found: C, 48·8; H, 5·7; S, 10·2. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7; S, 10·1%). On titration with sodium metaperiodate 1·1 mols. of oxidant were taken up.

2 : 3-*Anhydro*-α-*methyl*-l-*ribopyranoside*.—Prepared from 2-*p*-tosyl α-methyl-*l*-arabinoside (3·8 g.) in a manner similar to that described above for the β-isomer, the *anhydro-compound* (1·7 g.) was obtained as a syrup which crystallised on being kept for a few days in a desiccator and then had m. p. *ca.* 73° (sealed tube); $[\alpha]_D^{18}$ −145·1°±3° (*c*, 1·9 in chloroform) (Found: C, 49·2; H, 6·9. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

When the anhydro-compound (1·7 g.) was treated with methanolic sodium thiomethoxide and the product refluxed in alcohol with Raney nickel as described for the β-isomer, a hygroscopic syrup (1 g.) was obtained which distilled at 100—105° (bath temp.)/10^{-3} mm. and had $[\alpha]_D^{18°}$ −141·8°±1° (*c*, 2·48 in chloroform) (Found: C, 48·0; H, 8·0. Calc. for $C_6H_{12}O_4$: C, 48·6; H, 8·2%). It gave a weak green

Keller–Kiliani reaction and on titration with periodate took up *ca.* 0·3 mol./mol. That it contained 3-deoxy-α-methyl-*l*-xylopyranoside as its major constituent was proved by hydrolysis with 0·5N-sulphuric acid (specific rotations: after 20 minutes in the cold, −116°; after 30 minutes' heating, −3·4°; after 45 minutes' heating, +4·5° constant) when a syrupy sugar was obtained (Found: C, 44·4; H, 7·7. Calc. for $C_5H_{10}O_4$: C, 44·8; H, 7·5%). Warmed with *p*-nitrophenylhydrazine the sugar yielded 3-deoxy-*l*-xylose *p*-nitrophenylosazone, m. p. 254° undepressed in admixture with an authentic specimen (m. p. 254—256°) prepared above from the β-methylglycoside; no other crystalline material was isolated.

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184. *An Experimental Study of the Alkylation of Aromatic Amines using* (1) *Aluminium Alkoxides and* (2) *Alumina with Alcohols.*

By J. CAMPBELL EARL and NOEL G. HILLS.

The alkylation of aniline salts and complexes by means of aluminium alkoxides has been explored, and the influence of various anions and cations present on the rate of alkylation roughly examined. The vapour-phase methylation of methylaniline with methanol in the presence of alumina has also been studied in some detail, together with the effect on the rate of *N*-alkylation and on the tendency towards nuclear alkylation of the addition to the catalyst of various metallic salts.

THE demand for *N*-alkylated amines for war purposes led the authors to a review of alternative methods of alkylation which might be preferable in some respects to those at present used industrially. Some of the experimental results obtained with two such methods are described here. Not enough evidence is available to indicate whether the two processes under consideration differ fundamentally from one another or whether either or both of them involve the same reacting entities as the other known alkylation processes. It would therefore be premature to introduce a theoretical discussion at this stage. The catalytic action of alumina presents many points of interest which have often been discussed in the literature. Further information will no doubt be gained from a strictly quantitative study of the vapour-phase alkylation process. Requirements of such a study include rigid temperature control and a constant rate of passage of the reaction mixture over the catalyst. The considerable mechanical difficulties involved in meeting these requirements are gradually being overcome and it is hoped that the experimental results eventually obtained will be precise enough to justify theoretical treatment. Meanwhile, many of the facts brought to light during our preliminary studies seem to be of sufficient interest to describe here.

(1) *Alkylation of Aniline Salts and Complexes with Aluminium Alkoxides.*—Lazier and Adkins (*J. Amer. Chem. Soc.*, **1924**, **46**, 741) described the successful alkylation of aniline by heating it with the requisite aluminium alkoxide in a sealed tube at 250—350°. It is possible, however, to alkylate salts of aniline or aniline–metallic salt complexes under atmospheric pressure with aluminium alkoxides at considerably lower temperatures than those needed for aniline itself. The following table summarises a series of experiments in which various aniline salts were mixed with four times the amount of aluminium ethoxide required for complete diethylation and heated under a reflux condenser for several hours. The ease of alkylation of the iodide is

Salt.	Temp.	Time, hours.	Primary base in product, %.
$Ph{\cdot}NH_3Cl$	184°	5	91·8
$Ph{\cdot}NH_3Br$	184	5	46·7
$Ph{\cdot}NH_3I$	184	5	2·4 *
$Ph{\cdot}NH_3Br$	198	5½	6·3
$(Ph{\cdot}NH_3)_3PO_4$	198	5½	91·3
$(Ph{\cdot}NH_3)_2SO_4$	240	5	30·0

* Tertiary base 18·6%.

remarkable but is in agreement with a recorded observation that the direct action between alcohols and aniline is catalysed by iodides (Brit. Pat. 145,743).

Complexes of aniline with metallic salts can also be ethylated by a similar procedure, but the reaction does not take place as readily as with the anilinium salts:

Complex.	Temp.	Time, hours.	Primary base in product, %.
$CdSO_4,2Ph{\cdot}NH_2$	240°	5	69·8
$ZnSO_4,2Ph{\cdot}NH_2$	240	5	80·3
$ZnCl_2,2Ph{\cdot}NH_2$	240	5	56·2
$ZnBr_2,2PH{\cdot}NH_2$	240	5	41·8
$NiCl_2,2Ph{\cdot}NH_2$	240	5	90·3

It is evident that both cations and anions have an influence on the rate of alkylation.

The addition of sodium halides to reaction mixtures containing anilinium halides generally increased the rate of alkylation:

Anilinium salt.	Added salt.	Temp.	Time, hours.	Primary base in product, %.
$Ph{\cdot}NH_3Cl$	NaCl (1 mol.)	184°	5	44·1
$Ph{\cdot}NH_3Cl$	NaCl (2 mols.)	184	5	27·4
$Ph{\cdot}NH_3Br$	NaBr (1 mol.)	183	5	43·6
$Ph{\cdot}NH_3Br$	NaBr (1·5 mols.)	184	5	34·3

Some experiments on the *n*-butylation of aniline hydrochloride were made in which the different sodium halides were used as catalysts:

			Composition of basic product:		
Na halide per mol. of $Ph{\cdot}NH_3Cl$.	Temp.	Time, hours.	Primary, %.	Secondary, %.	Tertiary, %.
NaCl (1 mol.)	198°	16	65·1	34·9	—
NaBr (1 mol.)	198	10	43·3	48·7	8·0
NaI (1 mol.)	198	10	3·3	64·0	32·7

The following routine was adopted for isolating and examining the products from all experiments. The reaction mixture was mixed with a concentrated solution of sodium hydroxide and steam-distilled until no further oil came over. The distillate was extracted thoroughly with ether, and the ethereal solution dried with sodium sulphate. After removal of the ether the bases were distilled. If the distillation temperature indicated that no high-boiling fraction was present, the absence of important amounts of tertiary amine was assumed and no attempt was made to estimate it. Aniline in the product was determined by taking advantage of the fact that it forms a stable complex $CdCl_2,Ph{\cdot}NH_2$ precipitated when it is shaken with a saturated aqueous solution of cadmium chloride. The secondary and tertiary bases do not form water-stable complexes with cadmium chloride. For the actual estimation about 1 g. of the mixed bases was weighed in a 25-ml. graduated flask and 20 ml. of light petroleum (b. p. 40—60°) added with just sufficient 1 : 4-dioxan to form a homogeneous solution. The volume was then made up to 25 ml. with more light petroleum. Then 2 ml. of this solution, or more if the aniline content was low, were run into a small separating funnel and shaken with 3 ml. of saturated cadmium chloride solution. The white complex salt was immediately precipitated together with some cadmium chloride. Generally, most of the precipitate adhered to the wall of the funnel. The liquid was run off through a fritted-glass filter, and the precipitate remaining, partly in the funnel and partly on the filter, was washed with a little light petroleum. The precipitate was then dissolved in 10% hydrochloric acid and titrated with standard bromide–bromate solution and thiosulphate, and the result calculated as aniline. When the preliminary distillation showed the presence of much tertiary amine the above procedure was supplemented by an acetylation of the total bases with a known weight of acetic anhydride and determination of the amount unused after half an hour by decomposition with water and titration with alkali.

(2) *The Vapour-phase Methylation of* N-*Methylaniline by Methanol in the Presence of an Alumina Catalyst.*—Mailhe and de Godon (*Compt. rend.*, 1918, **166**, 467, 564; 1920, **171**, 1154; 1921, **172**, 1417) successfully alkylated aromatic amines by passing the mixed vapour of the amine and the requisite alcohol over a heated alumina catalyst. The reaction was further studied by Schujkin, Balandin, and others (*J. Gen. Chem. Russ.*, 1934, **4**, 1444; *J. Physical Chem.*, 1935, **39**, 1192), especially in respect of the effect of other oxides in admixture with the catalyst. In general, the other oxides diminished the activity of the catalyst, but were sometimes beneficial in inhibiting side reactions.

The large-scale manufacture of alkylated anilines by vapour-phase catalytic methods was successfully practised during the war. With suitably chosen catalysts, much lower temperatures than those specified by the above-mentioned workers (350—400°) were effective in bringing about a high degree of alkylation. It was, therefore, of interest to study the reaction more closely and especially to search for promoters which would increase the activity of the catalyst. To enable large numbers of experiments to be performed in reasonable time, their scale was kept as small as possible. The methods used for the analysis of the products were chosen for their rapidity and reproducibility rather than for their absolute accuracy. The experiments here described were exploratory and only roughly quantitative and were intended to give the preliminary information needed for planning more strictly quantitative work on the reaction. However, they themselves led to definite and interesting conclusions, which justify their description at this stage.

The apparatus used was simple. The liquid mixture of alcohol and amine (with any miscible promoting agent, if used) was placed in a feed chamber terminating in a capillary which projected well into the catalyst tube. A finely adjustable pressure of nitrogen was maintained above the reaction mixture to regulate its speed of introduction, and a by-pass also admitted a regulated stream of nitrogen into the catalyst tube. The tube itself was 35 cm. long and 13 mm. in diameter and terminated in a beak to facilitate the collection of the products in a small flask. The temperature of the catalyst mass was observed by means of a thermometer immersed in it. The tube was heated in an electric furnace.

To avoid unnecessary complications in the analysis of the products, attention was concentrated on the second stage of the methylation of aniline, namely, the conversion of *N*-methyl- into *NN*-dimethylaniline. Accompanying this reaction there is also some nuclear alkylation, the amount of which varies considerably according to the catalyst and experimental conditions used. The principal nuclear alkylation product to be expected is *N*-methyl-*p*-toluidine because it is known that in the large-scale methylation and ethylation of aniline the nuclear by-products consist mainly of *N*-methyl-*p*-toluidine and *N*:*p*-diethylaniline respectively [private communication from F. Kaufler and (Miss) J. Fildes]. A rapid, approximate method of determining the amounts of *N*-methylaniline, *N*-methyl-*p*-toluidine, and *NN*-dimethylaniline in the presence of one another depends on a combination of acetylation and refractive-index measurement. The secondary bases can be determined by quantitative acetylation, and the sum of *N*-methyl-*p*-toluidine and *NN*-dimethylaniline by measurement of the refractivity of the mixed bases. The refractive indices ($n_D^{20°}$) of the three bases are: *N*-methylaniline, 1·5714; *NN*-dimethylaniline, 1·5587; *N*-methyl-*p*-toluidine, 1·5582.

The catalytic activity of alumina, it is well known, varies greatly with the method of preparation. For these experiments, with a few exceptions specifically mentioned, the catalyst was made by decomposing aluminium *n*-butoxide with water, and drying and heating the product at 400° for 2 hours. It was then broken up and sifted, the fraction passing a 10-mesh and retained by a 20-mesh sieve being used. The weight of catalyst used for each experiment was 3 g., occupying approximately 10 c.c.

When the effect of a promoter in the catalyst itself was being examined, a quantity equivalent to 0·5 g. of sodium iodide was dissolved in methanol or aqueous methanol and mixed with 3 g. of the alumina, the solvent being then removed by heating on a water-bath.

For each of the experiments tabulated below, a reaction mixture containing 2 g. of *N*-methylaniline and 0·6 g. of methanol was introduced during 3½ hours into the catalyst tube, heated at 250° unless otherwise specifically mentioned.

In view of the accelerating effect of iodides in the alkylation of aniline salts by aluminium alkoxides mentioned above, a series of experiments were made using iodine or iodides in the reaction mixture. The percentage of acetylatable bases in the product was determined and calculated as monomethylaniline. The same charge of catalyst was used for the whole series of 11 experiments.

Amt. of iodine or iodide added.	Acetylatable bases expressed as NHPhMe, %.	Amt. of iodine or iodide added.	Acetylatable bases expressed as NHPhMe, %.
(None)	73·0	None	59·0
0·5% CH_3I	67·5	None	64·0
0·9% CH_3I	57·2	None	70·0
1·0% NH_2PhMeI	46·5	1% I	56·5
1·5% NH_2PhMeI	46·5	1% I	49·3
None	52·0		

These results show that iodine and iodides have a strongly accelerating effect on the reaction and that the effect is retained by the catalyst for some time.

When *N*-methylanilinium chloride is added to the reaction mixture there is not a marked increase in *N*-alkylation but a certain amount of nuclear alkylation takes place. The catalyst in this group of experiments was that used on the manufacturing scale for the methylation of aniline.

$NH_2PhMeCl$ added, %.	NHPhMe in product, %, from refractivity.	Acetylatable bases, %, calc. as NHPhMe.	Diff. due to nuclear alkylation.
None	43	42	− 1
None	42	43	1
None	45	49	4
5%	38	43	5
None	25	40	15
None	31	43	12
None	38	44	6
None	38	45	7
2½%	38	44	6
2½%	39	41	2
2½%	38	53	15
None	38	47	9
None	37	43	6
None	43	42	−1

It is clear from the above two series of experiments that a lag must be expected when a promoter is introduced with the reaction mixture, the promoted catalyst not showing its full activity for some time. The second series also shows what degree of accuracy is to be expected from the method described for estimation of nuclear alkylation.

A third series of experiments shows the effect of adding to the catalyst itself various salts which might be expected to have some effect in increasing the activity of the catalyst or in promoting nuclear alkylation. Each group of four experiments, three at 250° and one at 290°, was done with one charge of catalyst, a fresh charge being then introduced for the next group.

Temp.	Salt added.	NHPhMe, %, from refractivity.	Acetylatable bases, %, as NHPhMe.	Diff. (nuclear alkylation).	Temp.	Salt added.	NHPhMe, from refractivity.	Acetylatable bases, %, as NHPhMe.	Diff. (nuclear alkylation).
250°	None	34·2	38·0	3·8	250°	$CoCl_2$	10·3	13·1	2·8
250	None	38·9	45·3	6·4	250	$CoCl_2$	9·9	19·0	9·1
250	None	41·2	41·9	0·7	250	$CoCl_2$	7·5	23·6	16·1
290	None	16·4	19·4	3·0	290	$CoCl_2$	17·9	70·9	53·0
250	NaCl	32·7	27·6	− 5·1	250	$MnCl_2$	10·4	11·1	0·7
250	NaCl	32·7	31·8	− 0·9	250	$MnCl_2$	6·8	20·4	13·6
250	NaCl	33·5	35·1	1·6	250	$MnCl_2$	9·0	25·2	16·2
290	NaCl	15·0	30·0	15·0	290	$MnCl_2$	0·0	60·6	60·6
250	NaBr	10·4	10·2	− 0·2	250	$ZnCl_2$	19·5	21·9	2·4
250	NaBr	11·8	21·2	9·4	250	$ZnCl_2$	18·0	—	—
250	NaBr	10·3	21·4	11·1	250	$ZnCl_2$	10·4	35·5	25·1
290	NaBr	0·6	58·4	57·8	290	$ZnCl_2$	6·8	71·1	64·3
250	NaI	17·7	15·6	− 2·1	250	$CdCl_2$	9·8	13·0	3·2
250	NaI	17·7	17·9	0·2	250	$CdCl_2$	3·5	23·8	20·3
250	NaI	13·3	11·7	− 1·6	250	$CdCl_2$	0·5	41·3	40·8
290	NaI	4·5	65·1	60·6	290	$CdCl_2$	42·0	71·4	29·4
250	$NiCl_2$	13·4	16·7	3·3	250	$FeCl_3$	4·5	25·0	20·5
250	$NiCl_2$	15·6	22·2	6·6	250	$FeCl_3$	15·0	43·7	28·7
250	$NiCl_2$	22·5	26·3	3·8	250	$FeCl_3$	16·4	40·5	24·1
290	$NiCl_2$	14·0	56·0	42·0	290	$FeCl_3$	15·6	58·2	42·6
250	$CuCl_2$	11·2	43·3	32·1	250	$SnCl_2$	9·0	21·8	22·8

Although the figures in the above table show certain obvious irregularities, and minor variations in the values in cols. 3 and 5 cannot be regarded as having any real significance, yet there are major trends which lead to useful conclusions. All the salts used, except sodium chloride, increased the activity of the catalyst at 250°. Raising the temperature from 250° to 290° increased the rate of alkylation with pure alumina and when sodium halides, manganese chloride, or zinc chloride was present; but cobalt and cadmium chlorides definitely depressed the rate of alkylation at the higher temperature. Whilst with pure alumina there is no significant amount of nuclear alkylation even at 290°, yet most of the added salts promoted nuclear alkylation at that temperature and sometimes at 250° also.

The practical experience gained with the simple apparatus showed clearly that for a quantitative study of the kinetics of the alkylation reaction it would require much modification. This work has been undertaken and will be described in a later paper.

The authors' thanks are due for the award of a Commonwealth Government Scholarship to one of them (N. G. H.).

THE UNIVERSITY, SYDNEY, N.S.W. [*Received, October 17th*, 1946.]

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185. *Reactions of Alkylisoformanilides. Part III. With Phenols.*

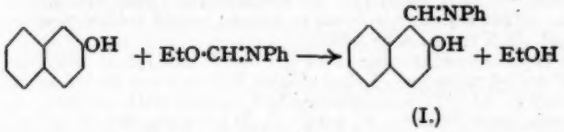
By EDWARD B. KNOTT.

Ethyl*iso*formanilide will react with polycyclic phenols containing a free, active *o*- or *p*-position to form hydroxyanils. Phenol does not react, but various substituted monocyclic phenols showed slight activity. The reagent may be formed *in situ* by using mixtures of ethyl orthoformate and aniline or diphenylformamidine. Replacement of the aniline by other aromatic amines leads to analogues. The reaction may be used as a qualitative test for reactive phenols since all the anils are highly coloured.

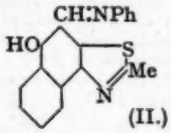
IN Parts I and II (*J.*, 1945, 686; *J.*, 1946, 120) of this series the activity of alkyl*iso*formanilides towards substances containing reactive or ionisable hydrogen has been described. It was of interest to determine the reactivity of these reagents towards polycyclic phenols, since the latter contain both ionisable and reactive hydrogen atoms.

Although phenol did not react with ethyl*iso*formanilide at temperatures up to 220°, the naphthols showed considerable reactivity even in boiling ethanol, and particularly at temperatures above 100°. The product from β-naphthol, an intensely yellow compound, was homogeneous, and was 2-hydroxy-1-naphthaldehyde anil (I). The orange solid from α-naphthol appeared to be a mixture of anils. The naphthols function therefore like substances containing a reactive methyl or methylene group, and the reaction is not dissimilar to the coupling with

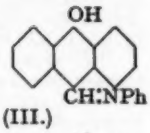
diazonium salts. A variety of phenols were then heated with the reagent, the formation of colour being taken as an indication of reaction. Amongst the monocyclic phenols, the cresols and polyhydroxybenzenes all gave yellow colours but no products were isolated. Polycyclic phenols with active *o*- or *p*-positions gave colours varying from yellow to red. Substances of this type not containing an active hydrogen in the *o*- or *p*-position, such as 1-bromo-2-naphthol,



(I.)



(II.)



(III.)

8-hydroxyquinoline, 4′-hydroxy-2 : 3′-dimethylnaphtha-1′ : 2′ : 4 : 5-thiazole, or 2-acetyl-1-naphthol, did not give any colour. Two other anils were isolated, *viz.*, *4′-hydroxy-2-methylnaphtha-1′ : 2′ : 4 : 5-thiazole-3′-aldehyde anil* (II) and *9-hydroxy-10-anthraldehyde anil* (III). The latter gave an intense red solution in aqueous sodium hydroxide. Its solution in acetic acid developed a similar intense red colour on the addition of concentrated hydrochloric acid, the colour fading rapidly as hydrolysis to the aldehyde occurred. The aldehyde differed in m. p. from that given in F.P. 648,069 for the product obtained from 9-hydroxyanthracene formomethylanilide and phosphorus oxychloride; but since in no case was reaction observed where both *o*- and *p*-positions were blocked, it is most likely that the aldehyde group in the present substance was introduced into the 10-position. Somewhat lower yields of anil may be obtained by the formation of the reagent *in situ*. This can be achieved (cf. Claisen, *Annalen*, 1895, **287**, 365) by fusing the phenol with mixtures of aniline or diphenylformamidine and ethyl orthoformate. Other aromatic amines may replace the aniline to give analogues.

Substance.	Colour.
Phenol	None
m-Cresol	Yellow
o- and *p*-Cresol	Faint yellow
Resorcinol	Yellow
Adrenalin	Red
o-Hydroxybenzylideneacetone	Yellow
2 : 5-Dihydroxydiphenyl	Orange-yellow
β-Naphthol	Yellow
α-Naphthol	Orange
1 : 5-Dihydroxynaphthalene	"
1-Bromo-2-hydroxy-naphthalene	None
1-Hydroxy-2-acetylnaphthalene	"
1-Hydroxy-4-phenylnaphthalene	Yellow
1-Hydroxy-4-furylnaphthalene-3-carboxylic acid	"
9-Hydroxyanthracene	Orange-red
4-Hydroxy-7-phenylcoumarone-6-carboxylic acid	Yellow
8-Hydroxyquinoline	None
2-Amino-6-hydroxypyridine sulphate	Orange
Aesculin	"
2-Hydroxy-3 : 4-benzfluorene	Red
4′-Hydroxy-2-methylnaphtha-1′ : 2′ : 4 : 5-thiazole	Orange-red
2-Acetamido-4′-hydroxynaphtha-1′ : 2′ : 4 : 5-selenazole	Red
4′-Hydroxy-2 : 3′-dimethylnaphtha-1′ : 2′ : 4 : 5-thiazole	None
4′-Hydroxy-2-methylphenanthra-1′ : 2′ : 4 : 5-thiazole	Red
1′-Hydroxy-2-methylphenanthra-4′ : 3′ : 4 : 5-thiazole	"
4′-Hydroxy-2-methylthionaphtheno-7′ : 6′ : 4 : 5-thiazole	Orange

The reaction may be used as a sensitive test for many phenols since the reaction products are highly coloured. The table indicates the colours obtained on boiling a small quantity of the phenol with an excess of reagent in a test-tube over a free flame.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.'s uncorrected.)

2-Hydroxy-1-naphthaldehyde Anil (I).—(a) β-Naphthol (14·4 g.; 0·1 mol.) and ethyl*iso*formanilide (14·9 g.; 0·1 mol.) were fused at 160° for 30 minutes, by which time the evolution of ethyl alcohol had ceased. Methyl alcohol (5 c.c.) was added to the melt. The yellow solid (17·0 g., 81%) crystallised as glossy needles, m. p. 92°, with an intense green fluorescence to ultra-violet light, when the methyl alcoholic solution was chilled, or shiny plates, m. p. 92°, with no fluorescence in ultra-violet light, if the same solution were allowed to cool (Found: C, 82·3; H, 5·4; N, 5·75. Calc. for $C_{17}H_{13}ON$: C, 82·55; H, 5·3; N, 5·65%).

(b) β-Naphthol (2·88 g.; 0·02 mol.), diphenylformamidine (2·92 g.; 0·02 mol.), and ethyl orthoformate (2·96 g.; 0·02 mol.) were fused at 150° for 60 minutes. After cooling, light petroleum was added and the whole shaken until the melt had solidified. From methyl alcohol (10 c.c.), 2·25 g. (46%) of the anil were obtained. If the ethyl orthoformate is omitted a yellow colour develops but the yield of anil is very low.

2-Hydroxy-1-naphthaldehyde p-Methoxyanil.—β-Naphthol (5·96 g.; 0·04 mol.), ethyl orthoformate (5·92 g.; 0·04 mol.), and *p*-anisidine (4·92 g.; 0·04 mol.) were fused at 145° for 60 minutes. The melt gave a crystalline *solid* on addition of methyl alcohol. From the same solvent it formed bright yellow needles, m. p. 111°, in 65% yield (Found: N, 5·1. $C_{18}H_{15}O_2N$ requires N, 5·05%).

9-Hydroxy-10-anthraldehyde Anil (III).—9-Hydroxyanthracene (3·84 g.; 0·02 mol.) and ethyl*iso*formanilide (3 g.; 0·02 mol.) were fused at 180° for 60 minutes. Ethyl alcohol (10 c.c.) was added to the red melt, and the orange-red crystalline *solid* (4·9 g., 82·5%) was collected and washed with alcohol. It formed garnet red crystals, m. p. 204°, from acetic acid (Found: N, 4·95. $C_{21}H_{15}ON$ requires N, 4·7%). *9-Hydroxyanthracene-10-aldehyde.* The anil (2 g.) was dissolved in boiling acetic acid (20 c.c.), and concentrated hydrochloric acid (4 c.c.) added. The intense red colour so formed slowly faded as the *aldehyde* crystallised. It formed flat, creamy needles, m. p. 230° onwards, from benzene (Found: C, 81·3; H, 4·4. $C_{15}H_{10}O_2$ requires C, 81·05; H, 4·55%).

4′-Hydroxy-2-methylnaphtha-1′:2′:4:5-thiazole-3′-aldehyde Anil (II).—4′-Hydroxy-2-methylnaphtha-1′:2′:4:5-thiazole (10·75 g.; 0·05 mol.) and ethyl*iso*formanilide (14·9 g.; 0·1 mol.) were fused at 170° for 60 minutes. On cooling, the orange melt solidified. It was ground with alcohol and well washed with the same solvent. It formed orange needles (13·2 g. = 86% yield), m. p. 228°, from benzene (Found: N, 8·5; S, 9·8. $C_{19}H_{14}ON_2S$ requires N, 8·8; S, 9·75%). The *aldehyde* was obtained by dissolving the anil (2 g.) in dioxan (30 c.c.), adding concentrated hydrochloric acid (10 c.c.) and water (10 c.c.), and heating for 30 minutes on the steam-bath. The solid was dissolved in an excess of 2N-sodium carbonate, filtered from a little unhydrolysed anil, and the yellow solution acidified. From ethyl alcohol it formed yellow-green needles, m. p. 160° (Found: S, 13·1. $C_{13}H_9O_2NS$ requires S, 13·2%).

KODAK LIMITED, WEALDSTONE, MIDDLESEX. [*Received, September 26th*, 1946.]

NOTE.

Infra-red Spectrum and Structural Diagnosis: Substituted Carbazoles. By R. E. RICHARDS.

THIS note describes an example, not only of the value to the organic chemist of infra-red measurements in structural diagnosis, but also of an experimental method developed in this laboratory for measuring the spectra of very small amounts of material. A sample was received for examination which had been formed by degradation of a substance of which the structure was not completely known. The specimen was a crystalline solid, only 1·5 mg. being available, and was suspected to be a mixture of carbazole and one or more of its methyl derivatives. It was required to determine which methyl derivatives were present and approximately in what proportions.

The experimental method had been mentioned by early workers (see also Thompson, *J.*, 1944, 191), but had not been widely used until it was developed in this laboratory in connection with recent studies on penicillin.

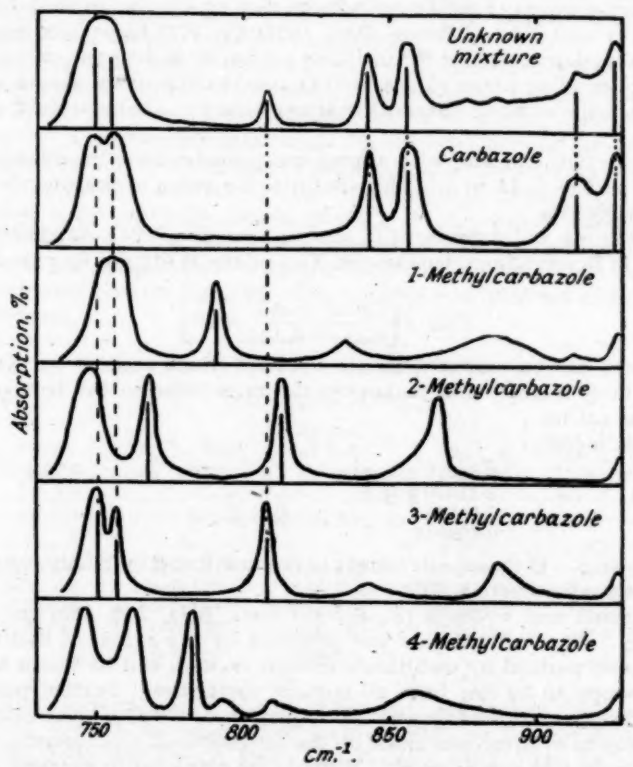
The specimen is ground to a very fine powder in a small glass or agate mortar. A suitable glass mortar can easily be made by rounding off a short piece of narrow glass tubing, and a piece of well-fitting glass rod with rounded end is used as the pestle; a small quantity of dry medicinal paraffin is then added to the powder, and the whole is ground to a smooth paste. This is transferred to a rock-salt plate, about 1·5 × 0·5 cm. in area, and another similar plate is placed on top. With the aid of a small spatula it is possible to prepare the specimen as a long narrow film between the plates, and almost any desired thickness can be obtained by appropriate manipulation, although it is obviously impossible to obtain an exact measure of the thickness of the absorbing layer. No clamping device or spacing washer is necessary, since the surface tension of the oil is sufficient to hold the plates together. The plates are placed on a flat platform so that the film lies exactly at a sharply focused image of the source of radiation, which is usually a Nernst filament. The sample, when thus prepared, causes very little scattering of the infra-red radiation, and a good spectrum can be obtained. The paraffin has strong absorption bands at about 720, 1375, 1460, 2850, 2925 cm.$^{-1}$, but in all other regions of the spectrum it shows no appreciable absorption except in very thick layers. When the spectrum has been measured, a large proportion of the sample can be recovered by extraction with a suitable solvent or by washing away the paraffin with a solvent which does not dissolve the specimen.

This method is often preferable to the alternative procedure of measuring the spectrum in solution; it is very simple, quick, and requires little of the sample. If it is desired to study such a small quantity of a specimen in solution, arrangements must be made to recover it from the solution in the absorption cell, and this requires a rather elaborate technique. This may, however, be essential, since more than one solvent must be used in order to cover the whole range of the infra-red spectrum, no single solvent being available which is completely transparent over the whole spectral range 1—14 μ. Such difficulties imply that in many cases the measurements in solution are impossible. In some circumstances it is useful to study the whole range of the spectrum of the solid as above, then to recover the sample, and to study some particularly interesting region in a suitable solvent which is transparent in that particular range.

The spectrometer used in this problem was a single-beam recording instrument, using a rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268).

Results.—The figure shows the spectrum, over the range 730—930 cm.$^{-1}$, of the unknown mixture,

together with the spectra of pure samples of carbazole and 1-, 2-, 3-, and 4-methylcarbazoles, obtained by the same method. Key bands are emphasised by the vertical lines. The presence of carbazole in the mixture is confirmed by the complete correspondence between the bands in the pure specimen and similar bands in the mixture. The complete absence of bands at either 790 or 782 cm.$^{-1}$ indicates the absence of 1- and 4-methylcarbazoles, whereas the band in the mixture at 808 cm.$^{-1}$ exactly corresponds to the strong key band of 3-methylcarbazole at this frequency—its weaker band at 886 cm.$^{-1}$ is lost between the strong bands of carbazole itself at 856 and 915 cm.$^{-1}$. The strong key bands of 2-methylcarbazole lie rather close to those of 3-methylcarbazole and make it impossible to establish the complete absence of the former, although if it is present, it can only be in very small amounts, for not a trace of the band at



767 cm.$^{-1}$ appears in the mixture, and the band at 808 cm.$^{-1}$ is not broadened noticeably towards 813 cm.$^{-1}$. It was therefore concluded that the unknown mixture contained mostly carbazole and 3-methylcarbazole. Comparison of the original spectrum with mixtures made from the pure materials shows that the unknown mixture contained between 5% and 12% of 3-methylcarbazole. A closer estimate of the relative proportions was not justifiable owing to the unknown differences in thickness and homogeneity of the different solid samples studied, but if larger amounts of material were available, solutions could be made up and compared with solutions of either the pure components or known match mixtures, so as to obtain a far more exact quantitative estimate.

I should like to thank Mr. K. H. Pausacker, who prepared the pure materials used in this investigation, and the Department of Scientific and Industrial Research for a maintenance grant.—THE PHYSICAL CHEMISTRY LABORATORY, SOUTH PARKS ROAD, OXFORD. [*Received, October 24th*, 1946.]

Twelfth Report of the Committee on Atomic Weights of the International Union of Chemistry.

By G. P. Baxter (Chairman), M. Guichard, O. Hönigschmid, and R. Whytlaw-Gray.

Owing to delays in communication it was impossible for the Committee to publish a report in 1942. The following report therefore covers the two-year period from September 30, 1940, to September 30, 1942. No changes have been made in the table, although the new values for samarium and ytterbium appear to be more reliable than those given in the table.

Carbon.—Murphy and Nier (*Physical Rev.*, 1941, **59**, 771) have determined with a mass spectrometer the abundance ratio of ^{12}C to ^{13}C in carbon from different sources to fall between 88·8 and 93·1, corresponding to the values 12·0117 and 12·0112 for the atomic weight of carbon. Both values support the existing chemical evidence that the atomic weight of carbon is very close to 12·01.

Oxygen.—Murphy (*ibid.*, p. 320) with a mass spectrometer finds the abundance ratio of ^{16}O to that of ^{18}O to be 500 ± 15 to 1. This confirms the value of Smythe, 503 ± 10, and the conversion factor 1·000275.

Fluorine.—Hutchison and Johnston (*J. Amer. Chem. Soc.*, 1941, **63**, 1580) have computed the atomic weight of fluorine from density and *X*-ray data of lithium fluoride and calcite, using the equation

$$\mathrm{LiF} = \left[\frac{\mathrm{CaCO_3} \times d_{\mathrm{LiF}}}{d_{\mathrm{calcite}} \times \phi_{\mathrm{calcite}}} \times R^3\right]$$

where ϕ_{calcite} denotes the volume of a calcite cleavage rhombohedron for which the distance between opposite faces is unity and R denotes the ratio between the true grating spaces for lithium fluoride and calcite.

The following data (20°):

d_{LiF}	2·64030 g./c.c.	Ca	40·075
d_{calcite}	2·71030 g./c.c.	Li	6·939
ϕ_{calcite}	1·09594	C	12·010
R	0·663045		

yield 18·994 for fluorine. If the atomic weight of calcium found by Hönigschmid and Kempter, 40·085, is used, fluorine becomes 18·996.

Zinc.—Hönigschmid and v. Mack (*Z. anorg. Chem.*, 1941, **246**, 363) have compared zinc chloride with silver. The zinc chloride was prepared by the action of hydrogen chloride on metal which had been purified by distillation in high vacuum and had been found by Gerlach by optical spectroscopy to be free from all metallic impurities. Further purification by two distillations in hydrogen chloride followed. Comparison of weighed quantities of the chloride with equivalent weights of silver was made by the conventional nephelometric method and the resulting silver chloride also was weighed. Weights are corrected to vacuum.

The Atomic Weight of Zinc.

Wt. of $ZnCl_2$, g.	Wt. of Ag, g.	$ZnCl_2 : 2Ag$.	At. wt. of Zn.	Wt. of AgCl, g.	$ZnCl_2 : 2AgCl$.	At. wt. of Zn.
Preliminary Series.						
2·26845	3·59116	0·631676	65·377	4·77125	0·475411	65·383
2·62763	4·15980	0·631672	65·376	5·52705	0·475413	65·374
4·62252	7·31790	0·631673	65·376	9·72300	0·475421	65·377
1·94421	3·07788	0·631672	65·376	4·08936	0·475431	65·380
3·81948	6·04655	0·631679	65·377	8·03341	0·475449	65·385
1·78151	2·82023	0·631690	65·379	3·74741	·0475398	65·370
1·94043	3·07193	0·631665	65·374	4·08179	0·475387	65·367
2·31880	3·67098	0·631657	65·372	4·87719	0·475430	65·382
Average		0·631673	65·376	—	0·475422	65·377
Final Series.						
2·08378	3·29875	0·631692	65·380	4·38304	0·475419	65·376
2·39497	3·79141	0·631684	65·378	5·03743	0·475435	65·391
3·25457	5·15229	0·631675	65·376	—	—	—
2·33816	3·70151	0·631678	65·377	4·91803	0·475426	65·378
2·23578	3·53951	0·631664	65·374	4·70270	0·475425	65·378
2·54724	4·03245	0·631686	65·379	5·35790	0·475418	65·376
2·32850	3·68614	0·631691	65·380	4·89779	0·475418	65·376
2·03634	3·22369	0·631680	65·377	4·28307	0·475439	65·382
Average		0·631681	65·378	—	0·475426	65·378

The average of all the experiments, 65·377, confirms the present value in the International Table, 65·38, but is 0·05 unit higher than that calculated from mass spectroscopic data, 65·33.

Molybdenum.—In the tenth report of the Committee the mean mass number as computed by Aston, 96·03, was stated to be in error. This statement is incorrect, and was due to an oversight of the fact that the summation of the percentages of the isotopes as given by Aston is 99·9 instead of 100. With the packing fraction $-6{\cdot}0 \times 10^{-4}$ and the conversion factor 1·000275 the atomic weight of molybdenum obtained from Aston's mean mass number is 95·95. A more recent determination of the abundance ratios by Valley (*Physical Rev.*, 1940, **57**, 945) yields 96·00 and 95·92 as the mean mass number and atomic weight respectively, while Hönigschmid and Wittner by analysis of the pentachloride found 95·95.

Samarium.—Hönigschmid and Hirschbold-Wittner (*Z. physikal. Chem.*, 1941, **189**, *A*, 38) have analysed anhydrous samarium trichloride. The samarium material had been purified by Feit and shown by Noddack by *X*-ray analysis to be of atomic weight purity. Further purification consisted of double precipitation of the oxalate followed by ignition to oxide in each case and crystallisation of the chloride from solution saturated with hydrogen chloride at ice temperature. The chloride was dehydrated by heating in a current of dry hydrogen chloride at gradually increasing temperatures, finally at 450°. Fusion was avoided since it was found experimentally that dissociation occurs at temperatures above the melting point. After being weighed, the chloride was dissolved and compared with a nearly equivalent weight of pure silver by the usual nephelometric method and the silver chloride was collected and weighed. Weights are corrected to vacuum.

The Atomic Weight of Samarium.

Wt. of $SmCl_3$, g.	Wt. of Ag, g.	$SmCl_3$: 3Ag.	At. wt. of Sm.	Wt. of AgCl, g.	$SmCl_3$: 3AgCl.	At. wt. of Sm.
$SmCl_3$ fused in HCl.						
3·27893	4·13279	0·79339	150·403	5·49102	0·59715	150·408
$SmCl_3$ dried at 450° in HCl.						
3·08886	—	—	—	5·17381	0·59702	150·354
2·96740	3·74054	0·79331	150·375	4·96975	0·59709	150·385
3·87834	4·88888	0·79330	150·372	6·49574	0·59706	150·371
3·37089	4·24914	0·79331	150·376	5·64562	0·59708	150·380
4·40134	5·54798	0·79332	150·380	7·37129	0·59709	150·385
Average		0·79331	150·376	—	0·59708	150·375

The average of all determinations, 150·38, is 0·05 unit lower than the present international value, 150·43, which depends on analyses of *fused* chloride by Stewart and James (*J. Amer. Chem. Soc.*, 1917, **39**, 2605) and Owens, Balke and Kremers (*ibid.*, 1920, **42**, 515). Although no change in the table is made at the present time, the new higher value seems to be a more reliable one.

Gadolinium.—Wahl (*Soc. Sci. Fennica, Commentationes Phys.-Math.*, 1941, II, **3**, 1) finds the isotopic constitution of gadolinium to be as follows :

Mass	152	154	155	156	157	158	160
Per cent.	0·2	2·86	15·61	20·59	16·42	23·45	20·87

These figures lead to the atomic weight 157·18 if the packing fraction $-1{\cdot}5 \times 10^{-4}$ is employed.

Ytterbium.—Hönigschmid and Hirschbold-Wittner (*Z. anorg. Chem.*, 1941, **248**, 72) have compared anhydrous ytterbium trichloride with silver. The starting material had been prepared by v. Bruckl by repeated electrolytic reduction and when subjected to *X*-ray analysis by Noddack was found to contain no other rare earths except lutecium, and this element only to the extent of 0·04%. The effect of this impurity would be to raise the atomic weight by only 0·001 unit. After repeated precipitation as hydroxide and oxalate, with intermediate ignition to oxide, the chloride was prepared and crystallised from a solution saturated with hydrogen chloride at 0°. Dehydration in preparation for weighing was effected by heating in a current of dry hydrogen chloride at gradually increasing temperatures up to 450°. Fusion was avoided since Hönigschmid had already found dissociation of the salt to occur above the melting point. Comparison with silver was effected in the usual way with the help of a nephelometer and the resulting silver chloride was collected and weighed. Weights are corrected to vacuum.

The Atomic Weight of Ytterbium.

Wt. of $YbCl_3$, g.	Wt. of Ag., g.	$YbCl_3 : 3Ag$.	At. wt. of Yb.	Wt. of AgCl, g.	$YbCl_3 : 3AgCl$.	At. wt. of Yb.
3·87107	—	—	—	5·94071	0·649934	173·108
3·82762	—	—	—	5·88965	0·649889	173·089
4·12899	4·78127	0·863576	173·117	6·35269	0·649959	173·119
2·58325	2·99157	0·863510	173·095	3·97473	0·649918	173·101
2·66672	3·08799	0·863578	173·117	4·10299	0·649946	173·113
2·58988	2·99916	0·863535	173·104	3·98478	0·649943	173·112
2·06819	2·39519	0·863476	173·085	—	—	—
2·42097	2·80349	0·863556	173·100	3·72495	0·649934	173·108
2·08411	2·41356	0·863500	173·092	3·20680	0·649904	173·095
1·72464	1·99732	0·863477	173·085	2·65378	0·649881	173·085
3·12912	3·62361	0·863537	173·089	4·81490	0·649883	173·086
3·92599	4·54636	0·863546	173·107	6·04062	0·649932	173·107
4·98554	5·77369	0·863493	173·090	7·67151	0·649877	173·083
Average		0·863526	173·098	—	0·649916	173·100

The average, 173·10, is 0·06 unit higher than that found by Hönigschmid and Striebel (*Z. anorg. Chem.*, **1933**, **212**, 385) with less pure material isolated by Prandtl. The new, higher value is evidently to be preferred although Wahl (*Naturwiss.*, **1941**, **29**, 536) by determination of isotopic abundances obtains the lower figure.

Mass	168	170	171	172	173	173	174	176
Per cent.	0·06	4·21	14·26	21·49	17·02	17·02	29·58	13·38

Thirteenth Report of the Committee on Atomic Weights of the International Union of Chemistry.[1]

By G. P. Baxter (Chairman), M. Guichard, and R. Whytlaw-Gray.

In the very regrettable death of Professor Otto Hönigschmid the International Committee on Atomic Weights has suffered a great loss. Professor Hönigschmid not only very actively promoted the work of the Committee but was himself responsible for a large portion of recent experimental work in this field.

Owing largely to difficulties of communication no report of the International Committee on Atomic Weights has been published for some time. The twelfth report was published only in Germany and France but essentially the same material appeared as the Report of the Committee on Atomic Weights of the American Chemical Society [2] at about the same time as the German Report.[3] Since no changes in the Table of Atomic Weights have been made since the Eleventh Report of the International Committee was published in 1941 until this year, this situation can have caused no serious difficulty. In the Table of Atomic Weights at the end of this report changes have been made in the cases of sulphur and copper. Attention is called to the fact that the atomic weight of common lead as determined from isotopic composition varies with the source over a range of 0·03—0·04 unit. At the present time it seems unwise to try to include values for the new elements Nos. 93—96, neptunium, plutonium, curium and americium.

Beryllium.—Johannsen (*Naturwiss.*, 1943, **31**, 592) synthesised beryllium chloride from beryllium oxide and carbon in a stream of chlorine and purified the product by sublimation without melting, first in chlorine, then in nitrogen, and finally in vacuum. The product was collected in sealed glass bulbs and was analysed in the usual way both by comparison with silver and by weighing the silver chloride, with the same resulting atomic weight 9·013 for beryllium. This result is somewhat lower than that found earlier by Hönigschmid and Birkenbach by analysis of the chloride, 9·018, and agrees closely with the mass spectroscopic value 9·0126.

Carbon and Nitrogen.—Casado (Thesis, University of Santiago, 1943) has redetermined experimentally the densities of oxygen, nitrous oxide, and methyl oxide at pressures of one atmosphere and below, as well as the deviations from Boyle's law at low pressures. Corrections of weights to the vacuum standard, for the contraction of the globes at pressures below one atmosphere, and for gravity were made. The average values from a large number of determinations are given in the following table.

	Oxygen.	Nitrous oxide.	Methyl oxide.
$1 + \lambda$	1·00089	1·00710	1·02574
d_1	1·428905	1·97747	2·10809
$d_{\frac{2}{3}}$	1·42844	1·97308	2·08987
$d_{\frac{1}{2}}$	—	—	2·08194
$d_{\frac{1}{3}}$	1·42799	1·96848	2·07330

If the densities plotted against the pressures are assumed to follow a straight line calculated by the method of least squares, the limiting densities and molecular weights are found to be as follows :

	Limiting densities.	Mol. wt.
Oxygen	1·42760	32·000
Nitrous oxide	1·96380	44·019
Methyl oxide	2·0561	46·088

From the molecular weights of nitrous oxide and methyl oxide the atomic weights of nitrogen and carbon may be calculated to be 14·009 and 12·020. If the values of $1 + \lambda$ are used together with the densities at one atmosphere the following results are obtained.

	d_1.	$1 + \lambda$.	d.	M.
Oxygen	1·428905	1·00089	1·42763	32·000
Nitrous oxide	1·97747	1·00710	1·96352	44·012
Methyl oxide	2·10809	1·02574	2·05518	46·066

from which the atomic weights N = 14·006 and C = 12·009 result.

Fluorine and Calcium.—In a series of papers, following the first by C. A. Hutchison and Johnston (*J. Amer. Chem. Soc.*, 1941, **63**, 1580), the method of calculating the atomic weights of

[1] Authors of papers bearing on the subject are requested to send copies to each of the three members of the Committee at the earliest possible moment : Prof. G. P. Baxter, Coolidge Laboratory, Harvard University, Cambridge, Mass., U.S.A.; Prof. M. Guichard, Faculté des Sciences, Sorbonne, Paris, France; Prof. R. Whytlaw-Gray, University of Leeds, Leeds, England.

[2] *J. Amer. Chem. Soc.*, 1943, **65**, 1443.

[3] *Ber.*, 1943, **76**, 35; *Bull. Soc. chim.*, 1944, **11**, 214.

fluorine and calcium from density and *X*-ray data has been continued by Johnston and D. A. Hutchison (*Physical Rev.*, 1943, **62**, 32), C. A. Hutchison (*J. Chem. Physics*, 1942, **10**, 489), D. A. Hutchison (*Physical Rev.*, 1944, **66**, 144), and D. A. Hutchison (*J. Chem. Physics*, 1945, **13**, 383). The atomic weights and densities used in the calculations of the last paper are as follows:

	Atomic weights.		Densities (20°).
C	12·0104	C	3·51540
Li	6·9390	LiF	2·64030
Na	22·9970	NaCl	2·16360
Cl	35·4570	KCl	1·98826
K	39·0960	$CaCO_3$	2·64030

The most reliable results as given in the last of the papers cited are as follows:

Calcium.

Reference substances.	Assumed atomic weights.	Atomic wt. of Ca.
Calcite, NaCl	Na, Cl, C	40·0851
Calcite, KCl	K, Cl, C	40·0851
Calcite, C (diamond)	C	40·0844
Calcite, LiF	K, Cl, Li, C, Na	40·0850
	Average	40·0849

Fluorine.

Reference substances.	Assumed atomic weights.	Atomic wt. of F.
LiF, KCl	K, Cl, Li	18·9967
LiF, NaCl	Na, Cl, Li	18·9967
LiF, C (diamond)	Li, C	18·9967
LiF, $CaCO_3$	Na, Cl, C, Li, K	18·9967
	Average	18·9967

The extraordinary concordance of the above results is of course dependent upon the values assumed in the calculation. If, for instance, the atomic weight of sodium is 22·994, the most recent value determined by Johnson, all molecular weights depending on that of sodium chloride will be lowered by 0·005%, and if the atomic weight of potassium is 39·098 instead of the one used, values depending on potassium chloride will be raised by 0·003%. The effect of this upon the atomic weight of calcium in the first two instances in the above table would be − 0·005 and + 0·002 unit. Because of the small molecular weight of lithium fluoride these uncertainties would affect the atomic weight of fluorine by only 0·001 unit. At the present time these results are to be considered as confirmatory rather than definitive.

Potassium, Aluminium, Magnesium and Sodium.—Batuecas, Casado, and Alonso (*Rev. Real Acad. Cienc. Madrid*, 1944, **38**, 349), using the method of Hutchison and Johnston (*J. Amer. Chem. Soc.*, 1941, **63**, 1580), have calculated the atomic weights of potassium, magnesium, aluminium, and sodium. Calcium and carbon are assumed to have the atomic weights 40·080 and 12·010. They find

$$K = 39{\cdot}091 \qquad Mg = 24{\cdot}317$$
$$Al = 26{\cdot}963 \qquad Na = \begin{cases} 22{\cdot}961 \\ 22{\cdot}989 \end{cases}$$

Silicon.—Ney and McQueen (*Physical Rev.*, 1946, **69**, 41) and Williams and Yuster (*ibid.*, p. 556) have obtained the following results for the isotopic proportions of silicon:

Isotope	28	29	30
Ney and McQueen	92·24	4·69	3·07
Williams and Yuster	92·27	4·68	3·05

If the packing fractions $-4{\cdot}86 \times 10^{-4}$, $-4{\cdot}54 \times 10^{-4}$ and $-5{\cdot}79 \times 10^{-4}$ are used the calculated atomic weight is 28·087. This value lies midway between that found by Baxter, Weatherill, and Scripture, 28·063, by comparing the halides with silver, and those obtained by Hönigschmid and Steinheil, 28·105, by the same method, and by Weatherill, 28·103, from the ratio of the tetrachloride to the dioxide.

Sulphur.—Hönigschmid (*Ber.*, 1942, **75**, 1814) has redetermined the ratio between silver and sulphur from the synthesis of silver sulphide, by essentially the method used by Hönigschmid and Sachtleben (*Z. anorg. Chem.*, 1931, **195**, 207), and with essentially the same result. Weighed quantities of fused buttons of pure silver were heated in a current of nitrogen and the vapour of purified sulphur, then in pure nitrogen at 250—300°. Below 300° the variations in the weight of sulphide were slight. Above 300° both the weight and the appearance of the sulphide were attended with variations. Vacuum corrections were applied.

It is unfortunate that owing to decomposition above 300° the silver sulphide could not be fused in order to make certain of complete conversion, but the fact that repeated heating of the silver sulphide in sulphur vapour at the lower temperature failed to effect appreciable alteration tends to favour the view that the above difficulty was not serious.

In the following table the weights of sulphide are the averages of the concordant observations when the sulphide was heated at various temperatures between 250° and 300°.

Wt. of Ag in vacuum, g.	No. of heatings with S.	Av. wt. of Ag_2S in vacuum, g.	Ag_2S : Ag.	At. wt. of S.
22·63155	2	25·99501	1·148618	32·0658
23·35829	4	26·82982	1·148621	32·0665
22·54273	1	25·89313	1·148621	32·0671
21·83830	2	25·08394	1·148621	32·0665
21·47088	2	24·66194	1·148623	32·0669
20·98104	4	24·09928	1·148622	32·0663
17·35371	6	19·93282	1·148620	32·0663
16·84347	16	19·34675	1·148620	32·0663
		Average	1·148620	32·0665

Richards and Jones (*J. Amer. Chem. Soc.*, 1907, **29**, 826) from the ratio of silver sulphate to silver chloride found 32·069, while Scheuer (*Sitzungsber. Akad. Wiss. Wien*, 1914, **123**, IIa, 1004) from the ratios $2Ag : SO_2 : Ag_2SO_4 : 2AgCl$ obtained the value 32·067. On the basis of the above two investigations by Hönigschmid, especially in view of the extraordinary concordance of the one reported here, there seems little doubt that the atomic weight of sulphur is very close to 32·066 if silver is taken as 107·880, and this value has been adopted for the table in place of the less precise one, 32·06.

Potassium.—Paul and Pahl (*Naturwiss.*, 1944, **32**, 226) have determined the relative abundance of ^{39}K and ^{41}K in common potassium to be $13{\cdot}96 \pm 0{\cdot}1$. With the packing fraction $-6{\cdot}1 \times 10^{-4}$ and the conversion factor 1·000275 the atomic weight of potassium is found to be 39·099. This agrees closely with the average of the most recent determinations of this constant, 39·097.* In the same way a sample of potassium partially separated by ideal distillation by Hevesy and Lögstrup was found to have the atomic weight 39·011. Hönigschmid and Goubeau, and Baxter and Alter both obtained the same value for this sample.

Copper.—Hönigschmid and Johannsen (*Z. anorg. Chem.*, 1944, **252**, 364; *Naturwiss.*, 1942, **31**, 548) have analysed cuprous chloride. Cupric sulphate was crystallised three times in the case of one sample, five times in the case of another. After electrodeposition on a platinum dish at 2 volts, the metal was dissolved in nitric acid and the nitrate crystallised and centrifugally drained. Decomposition to oxide in platinum followed. Spectroscopic examination by Dr. Schöntag revealed no impurities.

Conversion of the cupric oxide into cuprous chloride was carried out in the following operations: drying of the oxide in nitrogen at 200°, reduction in electrolytic hydrogen at 800°, conversion of the metal into cuprous chloride in nitrogen and chlorine mixtures, and resublimation of the cuprous chloride in nitrogen into a weighing tube, all in a quartz bottling apparatus. In the last two steps it was important to avoid a temperature above 600°.

Analysis followed, by solution in ammonia, oxidation to the cupric state with oxygen, acidification with nitric acid and comparison with silver in the conventional way.

Vacuum corrections were applied. In the following table two analyses believed by the authors to have been made with defective material are omitted.

Atomic Weight of Copper.

Wt. of CuCl in vacuum.	Wt. of Ag in vacuum.	CuCl : Ag.	At. wt. of Cu.	Wt. of AgCl in vacuum.	CuCl : AgCl.	At. wt. of Cu.
5·62293	6·12732	0·917682	63·542	8·14097	0·690695	63·545
5·27787	5·75129	0·917685	63·543	7·64158	0·690678	63·543
6·08707	6·63310	0·917681	63·542	8·81308	0·690686	63·544
4·84195	5·27638	0·917665	63·541	7·01062	0·690659	63·540
5·93141	6·46362	0·917661	63·540	8·58810	0·690655	63·539
5·74879	6·26460	0·917663	63·541	8·32345	0·690674	63·542
5·83204	6·35517	0·917684	63·543	8·44382	0·690687	63·544
6·54858	7·13604	0·917677	63·542	9·48162	0·690660	63·540
6·21862	6·77653	0·917670	63·541	9·00373	0·690672	63·542
6·03859	6·58024	0·917685	63·543	8·74323	0·690659	63·540
Average		0·917675	63·542	—	0·690673	63·542

* 39·096, Baxter and Alter, *J. Amer. Chem. Soc.*, 1933, **55**, 3270; 30·096, Hönigschmid and Sachtleben, *Z. anorg. Chem.*, 1933, **213**, 365; 39·100, Johnson, *J. Physical Chem.*, 1935, **39**, 781; 39·098, Baxter and Harrington, *J. Amer. Chem. Soc.*, 1940, **62**, 1836; 39·096, McAlpine and Bird, *ibid.*, 1941, **63**, 2960.

The outcome of this work, 63·542, is appreciably lower than that of Richards and his collaborators, 63·57, on which the International value has depended for some time, but is in close agreement with that obtained by Ruer (*Z. anorg. Chem.*, 1924, **137**, 101), 63·54, by reduction of cupric oxide, and with a recent isotopic analysis of copper by Ewald (*Z. Physik*, 1944, **122**, 487) which gives the value 63·53.

Selenium.—Hönigschmid and Görnhardt (*Naturwiss.*, 1944, **32**, 68) prepared pure selenium oxychloride by distillation in high vacuum in a glass still and collected the product in sealed glass bulbs. Analysis by comparison with silver chloride gave 78·961, while determintion of the silver chloride produced 78·963 for the atomic weight of selenium. This investigation confirms the present International value which depends on the earlier synthesis of silver selenide by Hönigschmid and Kapfenberger. The value calculated from the proportions of isotopes is 78·95 (Flügge and Mattauch, *Ber.*, 1943, **76**, *A*, 1).

Ruthenium.—Ewald (*Z. Physik*, 1944, **122**, 491) has determined the isotopic proportions of ruthenium to be as follows :

Isotopic weight	96	98	99	100	101	102	104
Per cent.	5·68	2·22	12·81	12·70	16·98	31·34	18·27

With the packing fraction $-6{\cdot}49 \times 10^{-4}$ and the conversion factor 1·000275 the atomic weight is calculated to be 101·04. Although Gleu and Rehm (*Z. anorg. Chem.*, 1937, **235**, 352) by analysis of the *purpureo*-chloride obtained the value 101·08, the uncertainties in their determination make it unwise to make any change in the Atomic Weight Table at the present time.

Silver, Bromine, and Potassium.—McAlpine and Bird (*J. Amer. Chem. Soc.*, 1941, **63**, 2960), by quantitative decomposition of potassium bromate, have found the ratio of potassium bromide to oxygen, and by comparison of the resulting potassium bromide with silver have found the ratio of these two substances. The results furnish a direct determination of the molecular weight of potassium bromide and an indirect determination of the atomic weight of silver.

Silver and bromine were purified by methods standard in atomic weight work. Potassium bromate was prepared from high-grade potassium hydroxide and an excess of bromine. After the solution had been boiled to remove excess of bromine and possibly iodine, the bromate was many times recrystallised until essentially free from bromide and sodium.

After prolonged drying in a vacuum the salt was further dried at 85—90° in the special weighed quartz decomposition flask, which was provided with a quartz filter disc to prevent loss of solid material, in a dry air stream, and was weighed. Very slow decomposition in a dry air stream followed, at gradually increasing temperatures up to 550°, until constant weight was obtained. During the decomposition the outgoing air stream was passed through a weighed phosphorus pentoxide tube to absorb residual water in the potassium bromate. In preliminary experiments it was found that decomposition of the bromate was complete and that the resulting bromide was neutral.

In the following table the weight of potassium bromate has been corrected for the water content as determined in each experiment. Vacuum corrections have been applied.

The Molecular Weight of Potassium Bromate.

$KBrO_3$, g.	KBr, g.	Ratio, KBr : O_3.	Mol. wt. of KBr.	$KBrO_3$, g.	KBr, g.	Ratio, KBr : O_3.	Mol. wt. of KBr.
10·67696	7·60833	2·47939	119·011	10·69361	7·62021	2·47941	119·012
7·54279	5·37493	2·47937	119·010	10·36524	7·38620	2·47939	119·011
7·44818	5·30753	2·47940	119·011	9·76351	6·95738	2·47935	119·009
9·72572	6·93055	2·47947	119·015	9·78441 *	6·97233	2·47942	119·012
9·62010	6·85524	2·47942	119·012				
8·50007	6·05711	2·47941	119·012		Average	2·47940	119·011

* Corrected in private communication from the authors.

Further evidence that the potassium bromide resulting from the decomposition was normal and free from moisture was obtained by comparing this bromide with silver in the conventional way by the nephelometric method. Similar experiments were made with potassium bromide prepared from pure bromine and potassium oxalate, and fused in nitrogen. Weights are corrected for air buoyancy.

If the established ratio of bromine to silver, 0·740786, is assumed, the atomic weights of bromine and potassium referred to silver as 107·879 are 79·915 and 39·096, respectively. All three values are in excellent agreement with those in the Table.

The Atomic Weight of Silver (KBr = 119·011).

KBr, g.	Ag, g.	Ratio, KBr : Ag.	At. wt. of Ag.*	KBr, g.	Ag, g.	Ratio, KBr : Ag.	At. wt. of Ag.*
			KBr from $KBrO_3$.				
5·37498	4·87217	1·103200	107·878	7·62092	6·90813	1·103181	107·880
5·30758	4·81110	1·103195	107·878	7·38622	6·69531	1·103193	107·879
6·93122	6·28281	1·103204	107·878	6·95738	6·30663	1·103185	107·879
6·85536	6·21410	1·103194	107·879	6·97265	6·32040	1·103197	107·878
6·05813	5·49155	1·103173	107·881		Average	1·103191	107·879
			KBr from $K_2C_2O_4$.				
5·08563	4·60984	1·103212	107·877	5·30793	4·81142	1·103194	107·879
4·94988	4·48694	1·103175	107·880	4·50218	4·08093	1·103224	107·876
5·64545	5·11714	1·103243 †	107·874	4·34549	3·93902	1·103191	107·879
5·38516	4·88142	1·103195	107·878	5·25160	4·76034	1·103199	107·878
5·92139	5·36755	1·103183	107·880	5·06778	4·59372	1·103197	107·878
4·62504	4·19245	1·103183	107·880		Average	1·103200	107·878

* Recalculated from authors' data.

† 1·103200 in the authors' paper.

Incidental to the investigation three syntheses of silver chloride from silver were made.

The Ratio of Silver to Silver Chloride.

Ag, g.	AgCl, g.	Ag : AgCl.	Ag, g.	AgCl, g.	Ag : AgCl
6·95254	9·23774	0·752623	6·63263	8·81249	0·752640
7·03045	9·34116	0·752631		Average	0·752631

The previously established value of this ratio is 0·752632.

Silver.—Paul (*Naturwiss.*, 1943, **31**, 419) has determined the proportions of the two isotopes of silver electrometrically with a mass spectroscope. The mean ratio from twelve determinations was found to be $\frac{^{107}Ag}{^{109}Ag} = 1{\cdot}080 \pm 0{\cdot}006$. If the packing fraction $-4{\cdot}8 \times 10^{-4}$ is used the atomic weight of silver is found to be 107·880.

Dysprosium.—Wahl (*Suomen Kem. Tied.*, 1942, **51**, 64; *Chem. Abstracts*, 1944, **38**, 5142) finds the following isotopic proportions for dysprosium.

Isotope	158	160	161	162	163	164
Per cent.	trace	0·1	21·1	26·6	24·8	27·3

The mean mass number calculated from these percentages is 162·581, and with the packing fraction $-1{\cdot}3 \times 10^{-4}$ and the conversion factor 1·000275 the atomic weight may be calculated to be 162·52. Owing apparently to the fact that the author's percentages total only 99·9, he calculates the incorrect value 162·42. Hönigschmid found, by analysis of the chloride, 162·46.

Hafnium.—Mattauch and Ewald (*Z. Physik*, 1944, **122**, 314) by photometric measurement of intensities in mass spectrographic plates have found the relative abundances of the hafnium isotopes to be as follows :

Isotope	174	176	177	178	179	180
Per cent.	0·18	5·30	18·47	27·10	13·84	35·11

The mean mass number calculated from these results is 178·54, and the atomic weight calculated with the packing fraction $+0{\cdot}2 \times 10^{-4}$ and the conversion factor 1·000275 is $178{\cdot}50 \pm 0{\cdot}01$. This result is appreciably lower than the atomic weight found by Hönigschmid and Zintl (*Ber.*, 1925, **58**, 453) in the usual chemical way. With two samples containing 0·57 and 0·16% of zirconium Hönigschmid and Zintl's results after correction for the zirconium content were 178·64 and 178·57.

Lead.—Permyakov (*Bull. Acad. Sci. U.R.R.S., Classe sci. chim.*, 1941, 581) has determined the atomic weight of lead from both Sadon galena and Khito-Ostrov uraninite by the conventional chloride–silver–silver chloride method. Weights are corrected to the vacuum standard.

Sadon galena.

Wt. of $PbCl_2$.	Wt. of Ag.	Ratio $PbCl_2$: 2Ag.	At. wt. of Pb.	Wt. of AgCl.	Ratio $PbCl_2$: 2AgCl.	At. wt. of Pb.
3·9615	3·0733	1·28900	207·20	4·0835	0·97010	207·19
2·2722	1·7628	1·28897	207·19	3·3423	0·97008	207·19
3·1425	2·4378	1·28907	207·21	3·2394	0·97009	207·19
	Average	1·28901	207·20	—	0·97009	207·19

Khito-Ostrov uraninite.

1·6599	1·2928	1·28396	206·11	1·7175	0·96646	206·14
2·3032	1·7939	1·28391	206·10	2·3834	0·96635	206·12
2·2354	1·7411	1·28390	206·10	2·3132	0·96637	206·12
	Average	1·28392	206·10	—	0·96639	206·13

Radium.—Attention is again called to the fact that in the most recent and accurate determination of the atomic weight of radium, by Hönigschmid and Sachtleben (*Z. anorg. Chem.*, 1934, **221**, 65), by conversion of radium bromide into radium chloride, no correction was made for the fact that weights of salt are too low since the temperature of the salts is always higher than that of the balance. The ratio involved is $RaBr_2 : RaBr_2 - RaCl_2$, in which the second term is far less affected than the first. In earlier work by Hönigschmid a positive correction of 0·01 unit was used. Although the mass spectrographic value is 226·05, identical with Hönigschmid and Sachtleben's uncorrected result, the application of the above rather uncertain correction produces a discrepancy of 0·01 unit.

INTERNATIONAL ATOMIC WEIGHTS, 1947.

	Symbol.	Atomic Number.	Atomic Weight.		Symbol.	Atomic Number.	Atomic Weight.
Aluminium	Al	13	26·97	Neon	Ne	10	20·183
Antimony	Sb	51	121·76	Nickel	Ni	28	58·69
Argon	A	18	39·944	Niobium (Columbium)	Nb	41	92·91
Arsenic	As	33	74·91	Nitrogen	N	7	14·008
Barium	Ba	56	137·36	Osmium	Os	76	190·2
Beryllium	Be	4	9·02	Oxygen	O	8	16·0000
Bismuth	Bi	83	209·00	Palladium	Pd	46	106·7
Boron	B	5	10·82	Phosphorus	P	15	30·98
Bromine	Br	35	79·916	Platinum	Pt	78	195·23
Cadmium	Cd	48	112·41	Potassium	K	19	39·096
Cæsium	Cs	55	132·91	Praseodymium ...	Pr	59	140·92
Calcium	Ca	20	40·08	Protoactinium ...	Pa	91	231
Carbon	C	6	12·010	Radium	Ra	88	226·05
Cerium	Ce	58	140·13	Radon	Rn	86	222
Chlorine	Cl	17	35·457	Rhenium	Re	75	186·31
Chromium	Cr	24	52·01	Rhodium	Rh	45	102·91
Cobalt	Co	27	58·94	Rubidium	Rb	37	85·48
Copper	Cu	29	63·54	Ruthenium	Ru	44	101·7
Dysprosium	Dy	66	162·46	Samarium	Sm	62	150·43
Erbium	Er	68	167·2	Scandium	Sc	21	45·10
Europium	Eu	63	152·0	Selenium	Se	34	78·96
Fluorine	F	9	19·00	Silicon	Si	14	28·06
Gadolinium	Gd	64	156·9	Silver	Ag	47	107·880
Gallium	Ga	31	69·72	Sodium	Na	11	22·997
Germanium	Ge	32	72·60	Strontium	Sr	38	87·63
Gold	Au	79	197·2	Sulphur	S	16	32·066
Hafnium	Hf	72	178·6	Tantalum	Ta	73	180·88
Helium	He	2	4·003	Tellurium	Te	52	127·61
Holmium	Ho	67	164·94	Terbium	Tb	65	159·2
Hydrogen	H	1	1·0080	Thallium	Tl	81	204·39
Indium	In	49	114·76	Thorium	Th	90	232·12
Iodine	I	53	126·92	Thulium	Tm	69	169·4
Iridium	Ir	77	193·1	Tin	Sn	50	118·70
Iron	Fe	26	55·85	Titanium	Ti	22	47·90
Krypton	Kr	36	83·7	Tungsten	W	74	183·92
Lanthanum	La	57	138·92	Uranium	U	92	238·07
Lead	Pb	82	207·21	Vanadium	V	23	50·95
Lithium	Li	3	6·940	Xenon	Xe	54	131·3
Lutecium	Lu	71	174·99	Ytterbium	Yb	70	173·04
Magnesium	Mg	12	24·32	Yttrium	Y	39	88·92
Manganese	Mn	25	54·93	Zinc	Zn	30	65·38
Mercury	Hg	80	200·61	Zirconium	Zr	40	91·22
Molybdenum	Mo	42	95·95				
Neodymium	Nd	60	144·27				

OBITUARY NOTICE.

ARTHUR LAPWORTH.

1872—1941.

ARTHUR LAPWORTH was born on October 10th, 1872, at Galashiels; his father was Charles Lapworth (F.R.S., 1888, Royal Medallist, 1891), the eminent first Professor of Geology in the University of Birmingham, who was a pioneer in laying the foundations of stratigraphy. After early education at St. Andrews and at King Edward's School, Birmingham, he graduated at Mason College and, as an 1851 Exhibitioner (1893—95), proceeded to the City and Guilds of London Institute, where the presiding genius was H. E. Armstrong. However, Lapworth came more directly under the care of F. S. Kipping, who was at that time in charge of the main organic laboratory.

Professor Kipping writes:

"From the very first it was obvious that Lapworth had the experimental skill, as well as the powers of acute observation and sound deduction which would ensure his success in scientific work, and that his vivid imagination and high intellect would take him far in his profession. Any one who made Lapworth's acquaintance could not fail to wish for closer ties, and although he was considerably my junior in age we soon became fast friends; perhaps it would be truer to say that our relationship, even in those early days, was rather that of congenial brothers. He became a frequent visitor at our house in South Kensington, where he often met Pope, Forster, and other workers in Armstrong's laboratories, and my wife soon shared with me the great pleasure of his friendship. During one vacation when he had made no holiday plans, we asked him to stay with us at Bridgwater: here it was that he met his future wife, Kathleen Holland, with whom during forty years he spent the rest of his life in peaceful and loving marital harmony."

To this may be added that Kathleen was the younger sister of Mrs. Kipping and of Mrs. W. H. Perkin; thus Mrs. Holland was the mother-in-law of three distinguished chemists and Fellows of the Royal Society.

His postgraduate course at the "Central" included crystallography under the late Sir Henry Miers and following this he worked with Armstrong on the sulphonation of ethers of β-naphthol and with Kipping on derivatives of camphor and camphene. So began two of his main interests in later research, the chemistry of camphor and the mechanism of aromatic substitution. His D.Sc. thesis,* submitted at the age of twenty-three, on the naphthalene topic was the occasion for a characteristic display of courageous independence. He refused to alter some sections of the theoretical treatment which his formidable professor had criticised.

Lapworth's first post (1895) was that of Demonstrator in Collie's laboratory at the School of Pharmacy in Bloomsbury. One joint paper (*J.*, 1897, **71**, 838) on picoline derivatives from this period bears the Collie stamp. In 1900 he went to the Goldsmiths' Company's Institute at New Cross as Head of the Chemistry Department (1906, Goldsmiths' College) and in 1909 became Senior Lecturer in Inorganic and Physical Chemistry and Schunck Fellow at the University of Manchester. Four years later he succeeded W. H. Perkin, jun., in the Chair of Organic Chemistry and in 1922 became Sir Samuel Hall Professor (primarily responsible for physical and inorganic chemistry) and Director of the Laboratories. The writer, first as a Junior Demonstrator and, after an interval of years, as Professor of Organic Chemistry, had the inestimable privilege of his friendship and collaboration. At lunch in the refectory and at many other times we exchanged ideas, often expressed on the back of envelopes by what Armstrong was pleased to call "noughts and crosses". During this latter period Mrs. Lapworth acted as his secretary in the department.

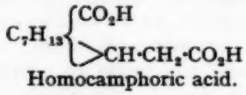
His last appointment demonstrates Lapworth's remarkable breadth and versatility; very few men in the twentieth century would be thought competent to hold in succession chairs of organic and physical chemistry. He retired in 1935 and was appointed Professor Emeritus. He was elected F.R.S. in 1910, served on the Council (1927—29), received the Davy Medal in 1931, and was an honorary LL.D. of Birmingham and of St. Andrews universities. These distinctions are mentioned with some uneasiness; high as they are they afford no measure of the achievement of a man whose influence on chemical philosophy was outstanding.

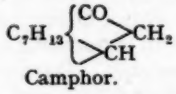
His modest disposition did not bring him into the limelight; he was not a showman, tending rather to disparage his wares; he made no dramatic discoveries such as to catch the public eye;

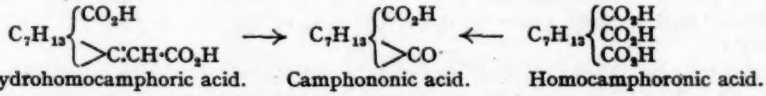
* "Sulphonic acids of betamethoxy- and betaethoxy-naphthalene." Thesis for D.Sc. (London), April, 1895.

he never flogged a dead horse and even left some promising live ones to fend for themselves. He investigated in order to learn something, to educate himself, and not with the primary object of producing elegant and finished scientific memoirs, though he did indeed leave many such on record. Much of his work seems, therefore, incomplete, and his output of over a hundred papers was, judged by some standards, relatively small. Yet the power of his genius triumphed and it is now possible to see how his ideas, always many years ahead of those of his contemporaries, played a leading part in the contribution which organic chemists have made to the revolution in chemical thought. The electronic theory of valency has made it possible to give a measure of precision to many of the suggestions he advanced on an electrochemical basis, but Lapworth's preparation of the ground was essential. During many years little attention was paid to his views; now they are the commonplaces of the textbooks.

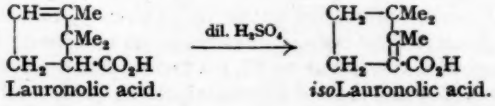
One of Lapworth's first major interests was the constitution of camphor and the way he attacked the problem was very significant. There are quite a number of ordinary papers on the detailed chemistry of derivatives; just the kind of thing that many workers in the field could, and did, produce. Certainly some of this material was of great importance and demonstrated his skill as an experimentalist, in particular his study of homocamphoric acid (*J.*, 1899, **75**, 986; 1900, **77**, 446, 1053) forged a vital link in the chain of evidence. In this investigation he showed that homocamphoric acid can be degraded to dehydrohomocamphoric acid and then to camphononic acid, which must be a *cyclo*pentane derivative because it could be synthesised by ketonisation of homocamphoronic acid. But his characteristic contribution was an idea—an


Homocamphoric acid.


Camphor.

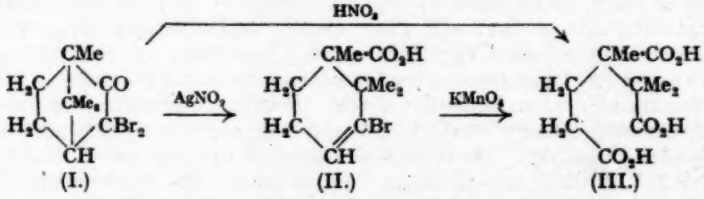

Dehydrohomocamphoric acid. Camphononic acid. Homocamphoronic acid.

interpretation of the chemistry of camphor which reconciled apparently conflicting data (*Brit. Assoc. Rep.*, Sec. B, Bradford, 1900). In other words he saw through the mist and by recognising the occurrence of a remarkable molecular rearrangement in the formation of *iso*lauronolic acid removed the chief stumbling block to the general acceptance of Bredt's camphor formula.


Lauronolic acid. *iso*Lauronolic acid.

The postulated intramolecular change was compared by Lapworth with the pinacol–pinacolone rearrangement and a similar explanation was also applied to the change of α- to β-campholenic acid, which was another source of confusion.

Homocamphoronic acid (III) itself and the stages of its production from αα-dibromocamphor (I) gave a great deal of trouble, as may well be understood when the direct formation of the acid by oxidation of (I) with nitric acid is considered (*J.*, 1899, **75**, 986). A carbon atom seems to get out of place.


(I.) (II.) (III.)

It was shown, however, that Forster's bromocamphorenic acid (II) is probably an intermediate product, and the very remarkable molecular rearrangement, (I) ⟶ (II), was suggested as the result of an extensive series of investigations (*J.*, 1899, **75**, 1134; 1900, **77**, 309, 446; 1902, **81**, 17). Lapworth carried these out in a systematic fashion by the careful study of the properties and reactions of the substances mentioned and, in addition, of camphonic acid, camphononic acid, and various bromo-lactones. It does not seem to have occurred to him to

attempt the synthesis of homocamphoronic acid, although that is perhaps due to the fact that the structures became clear only towards the end of a prolonged study.

The examples cited of the mobility of the camphor complex could be supplemented by many others and there is no doubt that the general acceptance of Bredt's formula owed as much to Lapworth's searching analysis as to the eventual synthesis of camphoric acid. Much later he prepared homocamphor (*J.*, 1920, **117**, 743), but the connecting link with later activities was perhaps his work on cyanocamphor and homocamphoric acid (*J.*, 1900, **77**, 1053). He was led to consider the problem of the addition of hydrocyanic acid to carbon compounds more generally and especially to the αβ-unsaturated ketones and the ketones and aldehydes themselves (*J.*, 1903, **83**, 995; *Proc.*, 1904, **20**, 245; *J.*, 1904, **85**, 1206—1214, 1355; 1906, **89**, 1819, 1869; 1907, **91**, 694, 977; 1910, **97**, 11; *Proc.*, 1911, **27**, 240; *J.*, 1911, **99**, 1877; 1928, 2533; 1930, 1976). The studies ranged from observations of the β-addition of cyano-groups to αβ-unsaturated ketones such as mesityl oxide, benzylideneacetone, carvone, and pulegone to the later, careful examination of the conditions of formation and the stability of cyanohydrins. There is little doubt that reflection on the mechanism of these reactions played an important part in directing his attention to the principle of " alternate polarities ". From the first he adopted ionic mechanisms, and a good illustration of his ideas is seen in the view he put forward of the course of the formation of benzoin from benzaldehyde (*J.*, 1907, **91**, 694). The production of a cyanohydrin was regarded by Lapworth as involving the direct attack of cyanidion on a carbonyl group :

$$>C{=}O + CN^- \longrightarrow >C\!<^{O^-}_{CN}$$

This he made very probable by a study of the effect of catalytic agents on the velocity of the addition (*J.*, 1903, **83**, 995) and by showing that the cyanohydrins are complex acids of which he was able to prepare the salts (*J.*, 1904, **85**, 1206). Thus by the action of potassium cyanide on benzaldehyde and camphorquinone he obtained crystalline potassium salts of the cyanohydrins. This view was confirmed by much subsequent research by Lapworth himself, by Bredt, and by Goldschmidt.

The second stage in the formation of a cyanohydrin is the decomposition of water, or an alcohol or acid, by the complex ion :

$$>C\!<^{O^-}_{CN} + H_2O \longrightarrow >C\!<^{OH}_{CN} + OH^-$$

He early recognised that these processes must be reversible and that normally an equilibrium will be set up. The theory explained very well why cyanohydrins are so advantageously prepared by the action of pure hydrocyanic acid on a ketone in the (necessary) presence of a small proportion of an alkaline catalyst, which may be potassium cyanide, or may even be derived from the glass container.

To complete the scheme of the benzoin synthesis it was assumed that benzaldehyde undergoes an aldol-like synthesis with mandelonitrile, and that the cyanohydrin of benzoin is relatively unstable. This was probable on theoretical grounds, and from analogies, but it was also experimentally demonstrated. The complete scheme was (*J.*, 1907, **91**, 694) :

$$C_6H_5{\cdot}CHO + CN' \rightleftarrows C_6H_5{\cdot}CH(CN){\cdot}O' \quad \text{(i)}$$

$$C_6H_5{\cdot}CH(CN){\cdot}O' + H^+ \rightleftarrows C_6H_5{\cdot}CH(CN){\cdot}OH \quad \text{(ii)}$$

$$C_6H_5{\cdot}CHO + C_6H_5{\cdot}CH(CN){\cdot}OH \rightleftarrows \begin{matrix} C_6H_5{\cdot}C(CN){\cdot}OH \\ C_6H_5{\cdot}CH{\cdot}OH \end{matrix} \quad \text{(iii)}$$

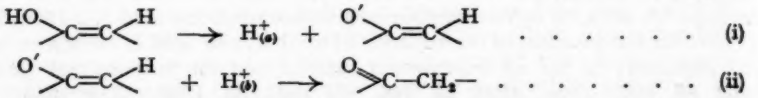
$$\begin{matrix} C_6H_5{\cdot}C(CN){\cdot}OH \\ C_6H_5{\cdot}CH{\cdot}OH \end{matrix} \rightleftarrows \begin{matrix} C_6H_5{\cdot}CO \\ C_6H_5{\cdot}CH{\cdot}OH \end{matrix} + HCN \quad \text{(iv)}$$

It will be noticed that Lapworth postulated reversibility of each stage. The theory has stood the test of forty years and is generally accepted as correct: undoubtedly it represented a landmark in the progress of our understanding of the course of chemical change.

Another outcome of the early camphor period was the use made of optical activity to study the phenomena of desmotropic, or tautomeric, change (*J.*, 1902, **81**, 1491, 1499, 1508; 1903, **83**, 114; 1904, **85**, 46; 1911, **99**, 1785). From the first Lapworth regarded these processes from the ionic point of view first advanced by Brühl in 1899, but in a less explicit form. He, however,

greatly extended the conception and supported it by many experimental researches carried on throughout his active career.

Mechanisms were invariably adopted which stressed the fact that the ions, particularly hydrogen ions, must often be regarded as coming in from outside and also as leaving for an unknown, and possibly remote, destination. Thus in keto-enol tautomerism catalysed by acids we have :



where the two protons *a* and *b* are not the same. Although these views, and perhaps some others that he advocated, were not completely novel, Lapworth made a better combination of them than any other chemist. His consistency and theoretical insight made a great impression on his contemporaries and exercised a powerful influence on the development of organic chemical theory. At a later stage he became interested in the mechanism of esterification and hydrolysis (*Proc.*, 1908, **24**, 100, 152, 153; *J.*, 1908, **93**, 2163, 2187; *Proc.*, 1909, **25**, 20; *J.*, 1910, **97**, 19; 1911, **99**, 917, 1417, 1427, 2242; 1912, **101**, 2249; 1913, **103**, 252; *Proc.*, 1914, **30**, 141; *J.*, 1915, **107**, 857; 1922, **121**, 76). Here again the emphasis was on hydrogen ion catalysis and the theory of acids and complex ions in various media. The researches were developed with the refinements of physico-chemical techniques and cannot usefully be summarised in the course of a short discussion. Many aspects of the work were unfinished and inconclusive but, taken as a whole, it must be admitted that this series of memoirs made an essential contribution to a subject which has excited great interest, and has of course been advanced by many other workers.

Another penetrating suggestion made by Lapworth concerned the mechanism of the bromination of ketones; the case chosen for study was acetone. The rate of bromination was found to be independent of the concentration of bromine and the process was catalysed by acids.

Lapworth suggested that the rate-determining change is the formation of enol from the acetone and that this is immediately brominated. The reaction is therefore autocatalytic due to the accumulation of hydrogen bromide. This view is accepted to-day for the acid-catalysed reaction, but other ions than hydrogen ions play a part and the complexity of the system is illustrated by H. M. Dawson's subsequent examination of the iodination of acetone. Anionotropic as well as prototropic reactions are in evidence. Considering the date (1913) of Lapworth's work (*Proc.*, 1913, **29**, 283) the advance he made was remarkable.

The conception of very rapid bromination of an enol was later utilised by K. H. Meyer for the analysis of mixtures of enols and ketones, for example, ethyl acetoacetate, under various circumstances. Lapworth often told the writer that he ought to have made this ingenious but obvious application. It is, however, doubtful whether full enolisation occurs, and it is not necessary to postulate it. Thus Leuchs has shown that an optically active ketone, the enol of which must be optically inactive, can be brominated without loss of activity. This recalls the observation of Kuhn and Albrecht that optically active *sec.*-nitrobutane yields an optically active sodium salt. Many other examples of Lapworth's concern with reaction mechanisms could be cited, including his early generalisations of the form of intramolecular changes (*Proc.*, 1895, **11**, 49; *J.*, 1898, **73**, 445; *Proc.*, 1901, **17**, 2; *J.*, 1901, **79**, 1265) and an examination of the synthesis of acetoacetic ester (*Proc.*, 1903, **19**, 189). Moreover he made kinetic studies of many reactions other than those mentioned and his work on the rate of oximation and the properties of oximes (*J.*, 1902, **81**, 549; 1907, **91**, 1133; 1908, **93**, 85) may be given in illustration.

Lapworth discovered many new reactions and transformations of which the following are among the more interesting.

Possibly his investigations of the addition of hydrogen cyanide to unsaturated ketones suggested that the quality of reactivity of the carbon of a carbonyl group can be transmitted to the β-carbon of an αβ-unsaturated ketone. If so, he may have argued, a carbonyl might activate a methylene group through a double bond. At any rate, in 1900 he made an experiment that must have had some such theoretical background.

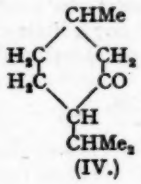
He found (*Proc.*, 1900, **16**, 132) that ethyl crotonate condensed with ethyl oxalate in the presence of sodium ethoxide as follows :

$$CO_2Et\cdot CO_2Et + CH_3\cdot CH{:}CH\cdot CO_2Et \longrightarrow CO_2Et\cdot CO\cdot CH_2\cdot CH{:}CH\cdot CO_2Et$$

The constitution of the product has since been confirmed; this was necessary in view of the possibility of the double bond migration to the βγ-position, followed by oxylation in the α-position. An extension was made later (*J.*, 1923, **123**, 1325).

Lapworth and Wechsler (*J.*, 1907, **91**, 1919) noted an anomalous reaction of cyanodihydrocarvone with amyl nitrite in the presence of sodium ethoxide. Further experiments revealed an interesting scission of ketones containing the group —CO—CH— under the same conditions. It may be assumed that a nitroso-derivative is first formed and that this adds the elements of alcohol to yield —CO·OEt + HON:C< (*J.*, 1908, **93**, 30).

Thus menthone (IV) yields (V) after hydrolysis of the product; pulegone (VI) gives (VII), the process involving the above-mentioned shift of a double bond. A simple model was provided (*J.*, 1911, **99**, 1882) by phenyl *iso*propyl ketone, Ph·CO·CHMe$_2$, which was found to be converted by amyl nitrite in alcoholic sodium ethoxide into benzoic ester, Ph·CO$_2$Et, and acetoxime, HON=CMe$_2$. This reaction has been applied to cinchoninone and affords in this and other cases a useful resource for the ring-fission of ketones.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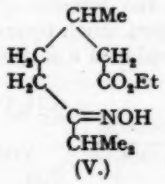
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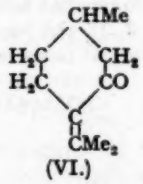
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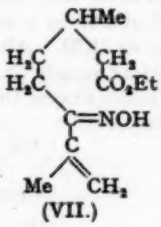
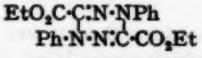

(VII.)

Another degradation was discovered when bromine was allowed to act on ethyl benzeneazoacetoacetate, CH$_3$·CO·CH(N$_2$Ph)·CO$_2$Et, when the acetyl group was eliminated and a so-called hydrizino-derivative, CBr(:N·NHPh)·CO$_2$Et, was produced (*J.*, 1905, **87**, 1854). When treated with alkalis, two molecules condensed to give ethyl diphenyldihydrotetrazinedicarboxylate,



These novel types of substances have not received much subsequent attention.

An interesting paper on sulphonic esters (*J.*, 1912, **101**, 273) describes some new reactions based on the idea that esters and sulphonic esters tend to undergo scission at the dotted line: R·CO$\dot{\div}$O—R′, R·SO$_2$·O$\dot{\div}$R′. It was found that olefins add the elements of sulphurous acid with the production of sulphonic acids (*J.*, 1925, **127**, 307). In the simplest case ethylene reacts with sodium hydrogen sulphite with formation of ethanesulphonic acid, which was isolated as the barium salt:

$$CH_2{:}CH_2 + NaHSO_3 \longrightarrow CH_2{\cdot}CH_2{\cdot}SO_3Na$$

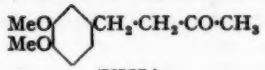
This reaction was rather unexpected; it underlines the abnormality of sulphur and recalls Posner's experiments on the addition of mercaptans to unsaturated substances.

At various times Lapworth paid considerable attention to improvements of preparative methods and to the prescription of satisfactory recipes. For example, he made really pure oleic acid (*Biochem. J.*, 1925, **19**, 7) and studied its quantitative oxidation to dihydroxystearic acid (*J.*, 1925, **127**, 1628, 1987). This is only one instance of his interest in the chemistry of the fats. He began work on sphingosine and cerebrone (*J.*, 1913, **103**, 1029) but never carried it far.

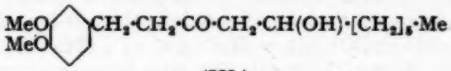
Other illustrations of the improvement of methods are the reductions of emulsified nitro-compounds (*J.*, 1921, **119**, 765, 768; 1925, **127**, 2970) whereby excellent yields of arylhydroxylamines were obtained, and contributions to *Organic Syntheses* (1927, **7**, 20; 1928, **8**, 99) based on his earlier work with McRae (*J.*, 1922, **121**, 1699, 2741). The details are characteristically elegant. An aldehyde such as benzaldehyde is brought into reaction with sodium cyanoacetate, previously made in the usual way; the addition of hydrocyanic acid and hydrolysis then afford a substituted succinic acid.

An unusual development for Lapworth was a study of natural products, in this case the pungent principles of ginger (*J.*, 1917, **111**, 77) and capsicum (*J.*, 1919, **115**, 1109). It is curious that E. K. Nelson, and also H. Nomura, published work on gingerol almost simultaneously with that of Lapworth, Pearson, and Royle. The work of Lapworth and his collaborators was the most comprehensive. The oleo-resin of Thresh, and of Garnett and Grier, methylated by means of methyl sulphate and alkali, yields a crystalline compound termed methylgingerol. This is decomposed by heat or alkali into methylzingerone, $C_{12}H_{16}O_3$, and aldehydes, of which the chief is *n*-heptaldehyde. Methylzingerone was proved by analysis and synthesis (*J.*, 1917,

111, 790) to be β-veratrylethyl methyl ketone (VIII) and the most plausible view of methylgingerol is expressed by the constitution (IX).



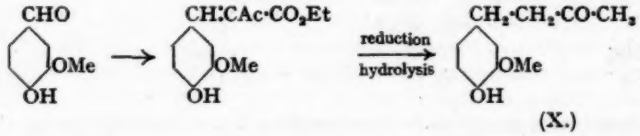
(VIII.)



(IX.)

Similarly the oleo-resin, before methylation, gave zingerone, $C_{11}H_{14}O_3$, which was proved by synthesis to be (X).

When, in the early Manchester days, one discussed synthetical projects with Lapworth, it was quite clear that he had some unusual way of deciding whether they would " go " or not. It turned out to be a scheme of alternating polarities in a chain of atoms, and the theory was published in 1920. Although somewhat hidden in the *Memoirs of the Manchester Literary and Philosophical Society* (lxiv, No. 3, 1), the paper evoked much interest, and not a little criticism. In later publications the theoretical basis was broadened and the principle developed with a



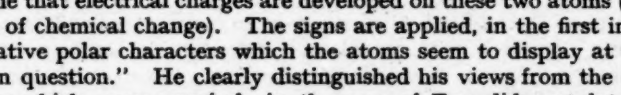
(X.)

conception of " virtual valencies " (*J.*, 1922, **121**, 416). Unfortunately this method of treatment was difficult to assimilate because of its form and, as the electronic interpretations, really equivalent to Lapworth's, were gradually adopted generally, this memoir of 1922 was almost forgotten.

Lapworth's main contribution to modern theory was his classification of reagents and his earlier work on reaction mechanisms, which were closely inter-related.

Starting from the two ionic types, he termed groups and molecular centres that exhibit reactive properties analogous to anions, *anionoid*, and those behaving like cations, *cationoid*. These expressions have exactly the same meaning as Ingold's *nucleophilic* and *electrophilic*. They implied electron donors, and electron acceptors, respectively. In regard to a few misconceptions, which arose in discussions, let Lapworth speak for himself (citations from *Mem. Manchester Lit. Phil. Soc., loc. cit.*). " The writer originally fell into the habit of labelling the atoms in reactive molecules with + and − signs as the result of his applications of the ionic theory to the reactions of carbon compounds and especially to those of ketones and allied carbonyl compounds. . . . It must be emphasised, however, that in attaching the + and − signs to the oxygen and carbon atoms no hypothesis is invoked, nor is it necessary, or even desirable, to assume that electrical charges are developed on these two atoms (except perhaps at the actual instant of chemical change). The signs are applied, in the first instance, merely as expressing the relative polar characters which the atoms seem to display at the instant of the chemical change in question." He clearly distinguished his views from the earlier theories of Fry and Vorländer which, more precisely in the case of Fry, did postulate actual alternate electric charges.

An example given was :



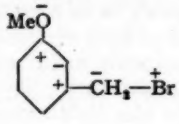
" It must now be evident from [corrected in reprints to *in*] the cases already dealt with that the whole order of alternating latent polarities is determined by the oxygen atom or atoms. . . . The extension of the influence of the directing, or *key-atom*, over a long range seems to require for its fullest display the presence of double bonds, and usually in conjugated positions, consequently the principle must find ample scope in the aromatic series where conjugation is the rule."

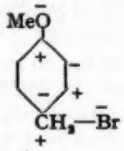
It was this aspect which was emphasised in the paper of 1922 (*J.*, 1922, **121**, 416) and the views there developed are, to all intents and purposes, identical with those advanced by the present writer starting from the conception of partial valencies. Both had some analogies with the systems of Thiele and of Flürscheim and in some applications gave identical results. There

was seen to be divergence, however, in other important respects and the origin of these became clear with the development of translations into the terms of the electronic theory of valency.

The working hypothesis of " labelling " from a key-atom gave rise to some interesting experimental work and an early example is that of Lapworth and Shoesmith (*J.*, 1922, **121**, 1391) on the methoxybenzyl bromides.

Thus the *m*- and *p*-isomerides are labelled from oxygen as key-atom :





The behaviour of these substances was found to harmonise with that predicted from the figures. It was known that Br in, for example, $\bar{O}{=}\overset{+}{C}{-}\bar{Br}$ is very readily replaced by OH and that Br in $\bar{O}{=}\overset{+}{C}{-}\underset{|}{\bar{C}}H{-}\overset{+}{Br}$ is unusually readily replaced by H. *p*-Methoxybenzyl bromide was much more easily hydrolysed to the related alcohol than was *m*-methoxybenzyl bromide, and in reductions to the tolyl methyl ethers, the *m*-isomeride was the more reactive.

Nowadays the properties of the *p*-derivative can be readily interpreted on a more precise electronic basis, but the *m*-derivative would be regarded as a benzyl bromide, lacking the special constitutive features of the *p*-type, and differing from benzyl bromide itself only as the result of the general electrical effect of the methoxy-group. In other words, it is the *p*-derivative that exhibits exceptional behaviour, and a comparison of benzyl bromide and *m*-methoxybenzyl bromide is required in order to estimate the significance of the contrast to which Lapworth and Shoesmith drew attention.

About this period (1922—26) an active controversy arose (cf. *J.*, 1925, **127**, 1742); this consumed much time and effort but need not be described in detail. Lapworth himself would be the last to desire these ephemeral writings to be resuscitated on account of their purely historical interest. It had at least one useful result in that the theory was more quickly moulded into its present form.

The chief subsequent events have arisen from the applications of quantum mechanics to organic chemical problems. These have provided a new calculus for the electronic theory of valency but have not rendered the older qualitative approach obsolete.

Lapworth's last scientific paper (*J.*, 1931, 1959) was most happily a collaborative effort with Professor C. K. Ingold. It was concerned with the problem of *m*-nitration of toluene. Competitive nitrations of toluene and benzene show that toluene is far more readily attacked than benzene. But in the nitration of toluene, only 4·4% of the *m*-derivative is produced. The question arises—does the methyl group activate the *m*-position, relative to the reactivity of benzene? Careful experiments showed that this is indeed the case, the disparity of toluene and benzene reactivity being sufficient.

There is little doubt that Lapworth would have continued to shed light on these and similar problems but unfortunately signs of his illness made their appearance early in the third decade of the century. He continued for some years to inspire his colleagues and collaborators by discussion and correspondence. Indeed it is true to say that throughout his life, though his publications are highly important, his generous help to others had an almost equal, if not greater, influence on the progress of science.

The world-wide recognition of Lapworth's genius and his abiding scientific reputation increases with the passage of time. It is now seen that his insight into chemical mechanisms, and his insistence on the electrochemical point of view at the molecular level, forged a necessary link in the chain of theory which now connects the most diverse phenomena.

In the laboratory one of his students, Dr. G. N. Burkhardt, gives the following picture. " He was skilful in devising and using the simple methods which he always preferred and, with a home-made cigarette in one corner of his mouth, and his head on one side, he would attack a new substance with reagents and a set of test-tubes. Using traces of material and a number of uncommon devices, he would find as much in a few minutes as might take hours to establish on a larger scale with more elaborate technique. As a teacher, lecturing on three main branches of chemistry in succession, he concerned himself to an unusual degree with the exposition of ideas, methods, and general principles, so that his lectures were most stimulating and valuable to his

better students, though they could be the despair of those whose tastes or abilities required only the easy catalogue of facts."

In his dealings with his fellow men he was selfless, generous to a fault, and completely straightforward and sincere. His scientific work occasionally brought him into controversy with exponents of older views, but this was always conducted with great dignity and the most careful choice of words. Incidentally he possessed an enviable command of language especially noticed in his writing, and a pretty and sometimes caustic wit, entirely free from any suspicion of malice. As administrator of his department and laboratory he showed firmness and wisdom, but this was not his real *métier* and it is a pity that a sense of duty compelled him to undertake responsibilities which turned out to last far too long. As already mentioned, the valuable help of Mrs. Lapworth lightened the load of routine for several years. The loyalty with which Lapworth was served and the undying devotion of all those who collaborated with him whether in teaching or research are the best testimony to his professional work and the University of Manchester owes much to his encouragement of young men of promise and to his guidance of the School of Chemistry during critical years.

A sensitive soul, always sparkling with vitality, all-embracing in his curiosity and interest, it is natural that he had many hobbies.

His father was a pianist and his mother and sister were accomplished singers. He himself played the violin and 'cello and was a lover of music, with sound and individual taste and a wide knowledge of the classics. He had little use for the modern forms. At New Cross he took part, as violinist, in chamber music and played in the College orchestra. When he came to Manchester Perkin asked him to share in his famous musical parties but there were too many violinists and Lapworth learned the viola. For many years he served on the Council of the Royal Manchester College of Music. He was a good dancer, was fond of the theatre, of films, radio, and the gramophone, and, in my time, he was a voracious reader of thrillers. Carpentry and microscopy were just two of his pursuits, and outside his chemistry his main scientific interests were astronomy, geology, and botany. He was an authority on British mosses and made a fine collection of them.

Holidays were spent in mountaineering and later in golfing and fishing. As a boy he started scrambling at St. Andrews and soon accompanied his father on geological expeditions to the mountains. At the age of eighteen he made a solitary ascent of the Petit Dent de Veisivi and later climbed Lliwedd and the Rosenlaui Engelhörner by several routes.

Much affected by the loss of his friend Humphrey Owen Jones and his wife on the Aiguille Blanche de Peteret, he never climbed again.

His fishing ground was chiefly the river Eden near Gosforth, and he was a member of the Yorkshire Anglers Club. Speaking of one of his friends he said : " The keenest angler I know—what a pity that he never catches fish ".

The outdoor life consorted well with his interest in nature, and it was K. J. P. Orton who introduced him to the study of birds. Orton, a recognised authority, was good with the field-glasses, but Lapworth's trained and sensitive ear enabled him to surpass his teacher in the recognition of birds by song. Birding with the Ortons was the *raison d'être* of many happy expeditions round Hayes Common, Keston, and in the Bangor district. Many years later the writer found in a St. Andrews " den " that Lapworth had not forgotten his craft.

The breadth of interest and joy in life which Lapworth showed in his recreations were characteristic of the man. In science, too, his temperament might have caused too wide a spread, but he was saved from this by self-discipline and by a dominant theoretical theme.

Lapworth's health, at least in later years, was never robust, and the exceptional strain of carrying the burden of the whole Department of Chemistry eventually broke it down. His long and distressing illness was borne with the greatest fortitude, but, until the very end, he never lost his interest and was able to enjoy the visits of his friends at intervals.

R. Robinson.

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